THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1937

ORIGINAL ARTICLES.

A CLINICAL LECTURE AS OF TWENTY-FIVE YEARS AGO.

By Henry A. Christian, M.D.,

PHYSICIAN IN CHIEF, THE PETER BENT BRIGHAM HOSPITAL; HERSEY PROFESSOR OF THE THEORY AND PRACTICE OF PHYSIC, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(Given in the Amphitheatre of the Peter Bent Brigham Hospital, May 27, 1937, on the Occasion of the 25th Anniversary of the Class of 1912 of the Harvard Medical School.)

It so happens that the twenty-fifth anniversary of the graduation of the Class of 1912 from the Harvard Medical School is a particular anniversary in my own medical life. In September, 1908, you of the Class of 1912 were beginning your medical careers. In that same year I was beginning the teaching of Medicine from the Chair of the Theory and Practice of Physic. This Chair at Harvard University has a past history indicating its great comfort. It is an historical fact that the Professors of the Theory and Practice of Physic all have looked on medical life from that chair for long periods of time. Benjamin Waterhouse, its first occupant, began early in life to sit in the chair and continued there for 30 years. Nobody has ever occupied it for less than 15 years, and the majority range between 15 and 30 years. If my activity continues through to my academic demise, I shall beat out old Benjamin by one year and establish a record for the chair.

This afternoon I am going to ask you to take yourselves back to the autumn of 1910 and place yourselves once again on the benches in the lecture room in the Medical School and let us re-discuss much as we did then a topic illustrated by a patient who was not present at the exercise, because in that year my patients were in South Boston at the Carney Hospital, and my amphitheatre for teaching was just across the street from here in the Harvard Medical School buildings.

We started in the early autumn of 1910 on a discussion of nephritis and I think it may be of interest today to pass around to you the classification of nephritis that we were then using.

CLASSIFICATION OF NEPHRITIS.

Lecture No. 1.

Pathological classification.	Clinical classification.
1. Acute degenerative nephritis	
2. Acute exudative glomerulonephritis	
3. Acute proliferative glomerulonephritis	
a. Capsular glomerulonephritis	Acute nephritis
b. Intracapillary glomerulonephritis	
4. Acute non-suppurative interstitial nephritis	
5. Acute suppurative interstitial nephritis	
6. Subacute glomerulonephritis	Subacute nephritis
7. Chronic parenchymatous nephritis	Chronic parenchymatous
Amyloid nephritis	
8. Chronic interstitial nephritis	Chronic interstitial
Arteriosclerotic	

I began my lecture by running over the classification of nephritis that had been given to you in the Department of Pathology and pointed out that a pathologic classification was not practical for application to every day clinical cases. Having myself taught in pathology and conducted the laboratory work for 3 years, I let you in on a little secret, namely, that the specimens of kidney, the sections of which you studied in your course in pathology, were accumulated with great difficulty from an enormous amount of material. Pathologists had worked hard to obtain those specimens for you, because ordinarily autopsies show a multiplicity of lesions in any single nephritic kidney. If one tries to apply to clinical work a pathologic classification such as the one you were taught, one becomes considerably confused. To avoid this, a large group (5) of the acute forms of nephritis in the pathologic classification were brought down clinically to just one, acute nephritis.

There were two forms of chronic nephritis in the pathologic classification; you will note the nomenclature of 25 years ago, interstitial and parenchymatous nephritis. In between the extremes of acute and chronic nephritis is a group, which was put down as subacute. This probably is closer in pathologic resemblances to the acute than the chronic. Clinically for these we used the same terms as in the pathologic classification, we spoke of subacute nephritis, chronic parenchymatous nephritis and chronic interstitial nephritis. Today, it is more fashionable to speak of chronic glomerular and chronic vascular or arteriolosclerotic nephritis.

Now let us turn to our case of 25 years ago.

He was a boy aged 15, with an essentially negative past history, except for an interesting sequence of childhood diseases. He had had mumps, measles and whooping cough all before he was 6 years of age. From 6 to 15

he had had no acute infectious disease of any sort. He first came into the hospital on September 21, 1908.

About 6 months before entry he had a septic condition in his knee. It was described as purulent arthritis. Judging, however, by the scar of the drainage incision and the perfection of the function of his knee joint, it is likely that he had merely an infection about rather than in his joint. He was well until September 15, that is, 6 days before he came into the hospital, when he had a severe attack of colicky pain in the abdomen. The pain persisted in a succession of attacks, which lasted anywhere from a few minutes to an hour or two, and were most severe in the right lower quadrant, though radiating to a certain extent over the entire abdomen. The bowels were loose rather than constipated. He knew of no recent dietary indiscretion.

He entered on the surgical service. His physical examination essentially was negative except for a slight degree of tenderness in his right lower quadrant brought about by pressure over it. The next morning his appendix was removed, and it was normal except for two small concretions. He stayed in the hospital from September 21 to October 1 and was sent home well.

On October 4, 3 days after he went home, while sitting up in a chair, he was seized with severe abdominal pain in the region of the liver, aching in quality, which lasted for half an hour. His bowels were constipated; he vomited a liquid, greenish material with pain. He was very sure that he had eaten nothing indigestible.

The symptoms continued until his second entrance to the hospital, on October 11. The pain, however, began to decrease so that he felt very much better on the day of entry than he felt previously; he even was strong enough to walk about the ward without any discomfort before he was put to bed. But the next morning he vomited again and had recurrence of pain now so intense that it caused him to draw his legs up over his abdomen.

He had been passing the usual normal amount of urine during his illness. He had lost a little weight.

He was rather undernourished and pale. His tongue was a bit coated. His radial arteries seemed, for his age, very definitely thickened. The lungs and heart seemed quite normal. There was slight edema of both ankles. Over both buttocks, and over the internal and external surfaces of the lower legs and feet there was a macular eruption, the macules being dark red to brownish in color and about the size of a pin head.

His urine showed albumin; the first specimen contained 0.25%, the second specimen 0.7%, the third specimen 0.6%. The specific gravity of the specimens were 1.009, 1.020, 1.023. The amount of urine excreted was somewhat decreased. Each specimen contained numerous finely and coarsely granular and epithelial casts, a few leukocytes and a few red cells. These represented the usual findings in his urine during his stay in the hospital.

The rash gradually decreased, disappeared, reappeared on October 22 and subsequently disappeared. On October 21 it was noticed that he had a little swelling of his face. The boy thought we were not giving him enough to eat, and his mother thought we were starving him, so she took him home. He left the hospital on October 22.

On November 12 he reappeared at the hospital now giving this story. Since leaving us he had stayed in bed part of the time, at first feeling fairly well. But presently his legs and scrotum began to swell. He had no headache, no return of the rash, no abdominal pain, no vomiting, no chills.

His urine now was a little scantier than it had been, a little more concentrated than previously, contained a little more albumin, but in the sediment had essentially the same cast picture.

The physical examination was very different. He had a coated tongue. The heart was perhaps a trifle enlarged on percussion. Over both backs, below the angle of the scapula, there was dulness on percussion, decreased breath sounds and distant, fine, crackling râles. His belly was distended, tympanitic in the upper part with dulness in the flanks. There was marked edema, beginning at his toes and going up over his abdomen with excessive edema over his scrotum. His weight, having been stated when he was well to be 108 pounds, was now 122 pounds; in a few days it increased to 123¾ pounds and then began to decrease as the fluid began to recede. By Thanksgiving time, November 26, he was fairly free from edema. He celebrated Thanksgiving well if not wisely. He made special arrangements on his own responsibility with the cook, and she behind the screen served him a regular Thanksgiving dinner, which he ate.

The evening of November 27 he had a little headache. The next day he did not want any food, and the idea of Thanksgiving dinner was very repugnant. At 2 A.M. that night he suddenly jumped out of bed, ran to the bathroom, was caught by the nurse and carried back to bed. He would not tell why he went to the bathroom. He slept the rest of the night from 2 A.M. on. At 7 A.M. he was found struggling in bed, with pupils dilated and twitching of the eyes, his eyes opening and shutting rapidly; he was thrashing his head from one side to another and at times not breathing, during which period he became cyanosed.

The condition was relieved by pulling the jaw forward as his throat became filled with mucus. He prespired freely. Between 7 A.M. and 9 A.M. he had 8 such convulsive seizures. He then remained quiet until about 2 P.M., when he had another convulsion. This quieted down, and he had no more until 8 P.M., when he had another and 3 the following morning. Subsequently he had no more.

During the period when he had his seizures, he became semicomatose, but gradually improved, cleared up mentally and 50 hours after the attacks started he was just about in the condition he was before they began. Nothing else particularly happened.

We kept him in the hospital until February 19. The edema by then had all disappeared, he was gaining weight and was feeling very well. The urine was not very different from what it was when he first came in, but it seemed wise to let him go home. His eye grounds showed nothing abnormal and I read in some of my lecture notes that I demonstrated to you 25 years ago an electric ophthalmoscope, showing how easy it was to use and how definitely it should be a part of the armamentarium of every doctor.

The middle of that following summer (June, 1909) he noticed that his urine was very dark in color and decreased in amount. This frightened him so that he came back into the hospital. He now weighed 118 pounds, looked well and had no edema. His urine contained a little albumin plus many casts. He stayed in the hospital for a few days and then went home.

He was seen again on October 5, 1910. Now his blood pressure had gone up. Up to this time it had been normal, now it was 150. No other changes were noted. He had now gained in weight to 134 pounds.

I saw him for the last time 2 years after his first admission, that is, in January, 1911. His blood pressure had returned to normal. His weight was 147½ pounds. His urine had a very slight trace of albumin and a very rare hyaline cast. He had been working steadily for 2 years in a machine shop running a lathe, and he felt perfectly well.

Now you notice that this history up to the note of October 5, 1910 antedated the time that I presented it to you (October 4 of that year). On that occasion we discussed this case. It may be interest-

ing to re-discuss it much as we did then, contrasting our views of it then with our present views.

One of the features of the case that seemed interesting was the possible effect of the appendectomy in the development of the nephritis. I spoke to you of the effects of ether in patients with or without renal disease and described to you a patient that I had had a few years before when I was inaugurating the clinical clerkship in Medicine at the Massachusetts General Hospital, which, by the way, I had the pleasure of starting with Dr. R. H. Fitz, in the autumn of 1905. With a group of students I observed a patient's specimen which, standing in the old fashioned urine glass that they used at the Massachusetts General Hospital, had a greenish, grayish sediment of about 1 inch at the bottom of the urine glass, which consisted almost entirely of granular casts. There was only the very slightest possible trace of albumin in this urine. The patient had received a considerable amount of ether the day before the urine was passed. The next day the urine was clear; there was not a trace of albumin and only an occasional hyaline cast. The next day the urine was entirely normal. I tried to leave you with the idea that an anesthetic might irritate the kidneys, but by and large one need not worry much about anesthesia as far as the kidney was concerned, unless there was some very serious preëxisting renal disturbance. This view I still maintain.

Another point that seemed of interest 25 years ago was the possibility of estimating by clinical observation the type of pathologic changes in the boy's kidney according to the classification of nephritis which we then were using. I pinned one of the members of the class down to offering the opinion that the boy's kidney was large and that the nephritis, essentially, was of the glomerular type. On the other hand, it seemed impossible clinically to predict minute microscopic changes as for instance whether the patient had, as Dr. Councilman used to say "an intracapil'lary proliferative glomerular lesion" or some other type of lesion. It was suggested that in all probability there also were degenerative changes in the epithelial cells, and that if one looked, one might find fat in the urine.

The skin lesions provoked much interest. Finally the class evolved a very interesting and modern point of view regarding their probable significance. We concluded that in the light of what was known, nephritis was not solely a disease of the kidney but also was a general systemic disease which involved the entire capillary system. Blood cells appeared in the urine due to weakening of the renal capillaries, and in similar fashion, edema appeared in the skin, weakened skin capillaries might give way and so cause the skin lesions such as were observed.

Together we analyzed carefully the history. We discussed the patient's abdominal pain, which apparently was not related to any abdominal pathologic process in the sense of appendix or gall-bladder

disease, and pointed out that abdominal pain is not a very uncommon symptom in acute nephritis and sometimes may also occur in the early stages of chronic nephritis; also we reminded ourselves that abdominal pain is not an unusual symptom in patients who have purpuric spots and that possibly this patient had a form of Henoch's purpura to explain his attacks. We knew that this patient had edema, that the edema cleared up and was followed by a uremic stage of 2 or 3 days' duration when convulsive seizures with coma appeared; that then he came out of this and gradually got better, his urine improved, and the albuminuria grew less. But a short time later, after a stage of apparent improvement, one day he noticed that his urine had become very dark and bloody again, and that the process had exacerbated, again to clear up until eventually the patient was working every day at a job and was seemingly healthy.

All this discussion naturally led to the matter of prognosis. In my opinion, it depended on whether this patient was developing a granular kidney or not. If so, the prognosis would probably be expressed by saying that the case would gradually change into the picture of chronic interstitial nephritis and the patient would probably live 4 or 5 years with it. Yet, on the other hand, it was perfectly possible for him to continue to excrete albumin and a certain number of casts and have very little change from now on in his renal condition. He even might stay clinically well almost indefinitely, because part of his kidney tissue would recover and become normal kidney and carry on the function of the kidney, although certain foci would remain injured, and these would furnish albumin and casts, while the good tissue would keep the machinery going effectively. On the other hand, I warned you to remember that subsequent acute illnesses would be likely to cause exacerbations. I believed it probable that this particular boy would develop chronic interstitial nephritis and go down hill fairly quickly; but I knew of people who had excreted albumin and casts and only after 20 or 30 years of this died of uremia.

Next we took up the mechanism of edema, and it is quite interesting, I think, to run over this subject, as told to you 25 years ago, and contrast it with the explanation which our present fourth year men give when they are asked what is the pathologic physiology of edema.

We emphasized the fact that the glomerulus in its diseased condition must interfere with the excretion of fluid and thereby theoretically should lead to what was spoken of as hydremic plethora. Against this theory was the fact that, as a rule, it was very difficult to demonstrate any increase of fluid in the blood, or hydremic plethora, in a patient with nephritis, and when "hydremic plethora" was demonstrable, it usually, though not always, failed to correspond with the edema. The patient who was not edematous might show plethora, and the patient who had edema might not show it.

Then we considered the relationship of edema to salt retention, and I cited to you cases in which the intake of salt seemed to control the accumulation or the disappearance of the edema fluid; but pointed out that that was not the whole answer, because there was a very definite group of cases that had marked salt retention and never had any edema at all. In the old fashioned terminology, such cases were those with chronic interstitial nephritis. I made a practical suggestion that in the management of an edematous patient, it was wise to try a restriction of salt, and if this method of dieting worked to lessen the edema, to continue with it; but that if it did not work, not to keep on with a saltless, unpalatable diet known to be accomplishing no good.

Another theory regarding the mechanism of edema was that the important cause lay in a generalized vascular lesion, a diseased condition of the small blood-vessels all over the body. In explanation of edema of such origin we could not offer very much from the clinical side, but we could offer a good deal from the experimental pathologic side. As I pointed out, in 1888, in Chittenden's laboratory in New Haven, Dr. Samuel Lambert, subsequently Professor of Medicine at Columbia University Medical School, Dean at the College of Physicians and Surgeons and Chief Physician at St. Luke's, and who by the way still is living, began to use uranium nitrate and found that this produced in rabbits nephritis of a form with which was associated edema, whereas other experimental substances would produce acute nephritis but without edema. Then I reminded you that in 1875 or 1877, about the time Dr. William Welch was working in Cohnheim's Laboratory, Cohnheim had shown that one could give animals things that produced kidney lesions, but such animals did not develop edema, even if a large amount of fluid was administered. But if one irritated the skins of such animals by rubbing on chloroform, the irritated part of the skin would become edematous. This observation suggested that some local skin condition on top of a background of renal disease made for edema. Finally, about 1908, Dr. Richard M. Pearce had been working in Philadelphia at the University of Pennsylvania on the problems of edema, stimulated somewhat by the well known interest of the late Dr. Weir Mitchell in snake bite. Dr. Pearce knew that if a rattle-snake bit an individual in the arm, let us say, the individual's arm swelled up and there developed an enormous amount of edema and hemorrhage in the tissues near the site of the wound. He found that if one injured the kidney of an animal with something like potassium bichromate that would not produce edema, and to the same animal gave snake venom short of producing hemorrhage, the vascular system was injured and edema developed.

From such observations, therefore, it seemed reasonable to believe that perhaps the most important part of the mechanism of edema was related to injury of the peripheral vascular system by toxic substances formed or not excreted in nephritis. That is exactly the

explanation that would be given today for the edema of the early stages of acute nephritis.

It is very interesting, that although in regard to salt retention we went into the idea of osmotic pressure of fluid and used the salt retention osmosis relationship to explain the edema in some patients, we had nothing to say about the plasma proteins, which now seem important in the mechanism of edema. My lectures were given to you in the autumn of 1910. In 1896 Starling had described the relationship of osmotic pressure of proteins to fluid exchange between blood-vessels and tissue spaces, pointing out that as the albumin content of the plasma was decreased, osmotic pressure changed, and the fluid exuded out of the vessels faster than it was taken up by the veins. Clinicians apparently paid no attention to Starling's work and made no use of it until much later. I certainly did not, notwithstanding the fact that Starling came over to this country 3 or 4 years before my lectures to you and gave a lecture on that particular subject.

It took 10 or 12 years more before physicians realized the importance of this physiologic idea, for it was not until 1920 or thereabouts that they began to talk of it. Leo Loeb in a very extensive review of the causes of edema published in 1923-1924 mentioned Starling's ideas, but did not think them especially important. Today in order to explain the formation of edema, we talk about capillary permeability, salt retention and now add the effect of variations of the plasma protein as part of the mechanism of edema, realizing that not one single factor, but combinations of varying factors lead to edema.

There is one more topic that we took up at the clinic 25 years ago, namely the frequency of high blood pressure in cases with chronic renal lesions. Dr. Roger I. Lee had very recently published a study calling attention to the relation of high blood pressure to the lesions in the kidney. We discussed his observations and came to the conclusion that the prime factor in hypertension was peripheral vascular constriction in some way related to the lesion in the kidney. This is about all one can say with certainty about high blood pressure in nephritis today, 25 years later.

It has been a great pleasure to me to welcome you back today and repeat for you again a clinical lecture on nephritis. Your faces are somewhat changed, perhaps, but not much more than has changed our physiological conception of chronic nephritis in 25 years. The more I have looked at each of you during this lecture, the more unchanged have each of you seemed to be. I now see smiles again that I used to see frequently. But today on the seats I do not see anybody asleep, while that was not a very uncommon experience 25 years ago. Perhaps this is an omen signifying your greater interest in medicine. I hope that many of you will be here at your fiftieth reunion to consider nephritis, edema and high blood pressure.

VACCINATION AGAINST EPIDEMIC INFLUENZA WITH ACTIVE VIRUS OF HUMAN INFLUENZA.*

(A TWO-YEAR STUDY.)

BY JOSEPH STOKES, JR., M.D.,

AIMS C. MCGUINNESS, M.D.,

PAUL H. LANGNER, JR., M.D.,

AND

DOROTHY R. SHAW, M.S.,

PHILADELPHIA, PA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital.)

THE studies reported here concern the results of intramuscular vaccination of human beings in large State Colonies with active virus of human influenza, covering the epidemics of respiratory infections of two winters, 1935–1936 and 1936–1937.

Since 1933 when Smith, Andrewes, and Laidlaw[4] first isolated in ferrets the W.S. virus from nasopharyngeal washings of an individual suffering from epidemic influenza, in practically all subsequent sharp outbreaks studied, viruses of closely similar antigenic properties have been isolated. Also during the past winter, 1936–1937, from a pandemic involving European countries, the British Isles, and the United States, closely similar viruses were isolated.

These viruses have not been found in the absence of influenza epidemics and when injected intranasally in ferrets and mice cause a disease which is practically identical with influenza of varying degrees of severity in human beings. When repeatedly injected into these animals by other routes than the respiratory tract, no disease is produced, but on the other hand an immunity to the disease is obtained. Following repeated injections of active influenza virus, it is as yet uncertain how long immunity remains.

The probable etiologic relationship of these viruses to influenza has been shown on human volunteers by Smorodintseff, *et al.*[5] when the great majority suffered attacks following inhalation of a virus-containing spray.

Magill and Francis[3] produced in the serum of the rabbit, a naturally immune animal, for a short period neutralizing antibodies specific only for the strain of virus injected. Later, however, cross

* These studies were assisted by a grant from the Bureau of Animal Industry, United States Department of Agriculture, and by the Lyophile Serum Fund donated by the Board of Managers of the Abington Memorial Hospital.

The ferret colony was obtained through a grant from the International Health Division of the Rockefeller Foundation, New York.

neutralizing antibodies appear in the serum with or without an additional intraperitoneal injection of virus. In these experiments the results "would suggest contrary to previously expressed opinion[1] that the swine virus comprises a more complex antigen than the human strains and that the common antigen which elicits the cross neutralizing antibodies is more effectively present in the swine virus."

Despite the demonstrated differences in the antigenic components of the influenza virus strains so far isolated, nevertheless, in a consideration of the production of immunity in the susceptible or in the nonsusceptible animal, it is significant that repeated injections by other routes than the respiratory tract of any one of the human strains isolated has given cross-protection against all of the other strains. For this reason the production of active immunity in human beings against epidemic influenza with one or more of the virus strains has appeared worthy of trial and has resulted in the studies previously reported[6] and in the present further extension of those studies.

Method of Vaccination. In our earlier studies both the human influenza virus of Francis (PR–8) and the swine influenza virus of Shope (S–15) were used for intramuscular injection. Berkefeld filtrates of suspensions of infected mouse lungs free as far as could be determined from any other organism pathogenic for man, were used as vaccines, whereas during the more recent studies active human virus (PR–8) grown on chick embryo tissue cultures, was used. The reasons for the use of active human virus rather than of inactivated virus for vaccination have been discussed previously.[6] In 1935–1936, a single colony* of approximately 800 individuals was available for study; in 1936–1937, four additional State Colonies and one private institution were made available, including in all slightly over 5000 individuals. In the winter of 1935–1936, 110 individuals were injected with active human virus (PR–8) and 138 with active swine virus (S–15) in mouse lung emulsion, while the rest of the colony (550) remained unvaccinated. In 1936–1937, all except 8† of those vaccinated during the previous winter season again received active human virus (PR–8) intramuscularly in the form of chick embryo tissue cultures, and in addition approximately one-third of each of the new colonies added to the study were vaccinated with the latter type of vaccine. In contrast to the first season, all vaccinations were performed during the fall and early winter at a time when respiratory infections were minimal.

The chick embryo tissue culture vaccine was grown in large oval culture flasks of 1 liter. A single 13-day chick embryo was finely divided in 200 cc. of Tyrode's solution to which the virus culture was added and the culture was incubated for 48 hours. Of this culture 2 cc. were injected intramus-

* We are indebted to the Department of Institutions and Agencies of the State of New Jersey for their interest and coöperation in these studies.

† On account of the discharge and deaths of a few inmates during the period of study, the numbers in the colonies mentioned throughout are necessarily approximate. Such changes were insufficient to interfere with the statistical analysis of the results, and occurred proportionately among vaccinated and unvaccinated inmates. For instance, in Colony N. L. among those whose vaccinations were completed on December 15, 1936, there were 10 who were not present in the Colony when the epidemic started on January 20, 1937. Slightly more than 275 individuals had been vaccinated so that the groups in Table 3 remained relatively unchanged.

cularly at weekly intervals for 3 doses. The potency of the virus culture was tested in mice before and after injections and a similar fourth dose was injected if any single batch of vaccine failed to show typical lung lesions in mice in a dilution of 1:1000. The method of giving intranasal instillations and of determining lesions in mice has been previously described.[6]

All of the inmates were housed in cottages, the first third alphabetically in each cottage being chosen for vaccination. In two of the colonies in which influenza epidemics later occurred there were also common dining and amusement halls which insured fairly close contact of all the inmates.

Results. Mild local reactions were noted at times when virus-infected mouse lung was used as the vaccine, and in one instance there was a rather severe local reaction. Such reactions were absent when the chick embryo virus vaccine was used, aside from mild soreness such as occurs from a similar injection of 2 cc. of human serum. In a very few individuals and usually within 24 hours following the second injection of the latter vaccine, a slight watery discharge from the nose and "stuffiness" were noted, resembling in some respects a common cold. This cleared rapidly and appeared to be a transient vasomotor response, possibly of an allergic nature. From one such individual, vaccinated in another institution in Philadelphia, nasopharyngeal washings injected intranasally into an anesthetized ferret gave no evidence of the presence of influenza virus. Such reactions* usually followed the second injection of vaccine, were afebrile, evanescent, and without generalized signs or symptoms. Neither among the 1700 vaccinated individuals nor among the 3300 unvaccinated who in each cottage were in quite intimate contact with those vaccinated, was there any evidence of respiratory infection as a result of the vaccination. During the period of vaccination of all colonies from October, 1936, to January 1, 1937, there were no epidemics of respiratory disease, and from the records of all colonies it was noted that during the last months of 1936 there was unusual freedom from respiratory infections. Because of the large number of mice required (approximately 11,000) for study of the neutralizing properties of the sera both before and after vaccination in 1935–1936,[6] a representative number of sera were obtained at similar intervals during 1936–1937 from all but one of the colonies studied. These neutralization tests will be reported later.

Clinical Results. Epidemics of influenza during 1936–1937 occurred in Philadelphia and in two of the colonies, N.L. and J., as shown by recovery of human influenza virus from nasopharyngeal washings through ferret passage. Probably also the disease occurred a little later in a few cottages of Colony S., although in so

* One of us, P. H. L., Jr., injected chick embryo tissue culture virus intradermally into a number of individuals known to be allergic to chicken and to egg, without any general reaction.

few individuals that nasopharyngeal washings were not obtained.* Colony S. is so large, about 1450 inmates, that a number of febrile respiratory infections may occur without assuming epidemic proportions. In Colony N.L. a similar epidemic had occurred during the previous season (February and March, 1936).[6] In this epidemic the human influenza virus was in all probability the causative agent since neutralizing antibodies appeared in the sera of unvaccinated children in the epidemic area around the colony during convalescence when none were present in their sera during the illness. Studies of the nasal and throat washings from the febrile cases in this epidemic were not sufficient to furnish significant data. This epidemic, previously reported, is summarized in this report (Table 1) since it has a bearing on the epidemic in the same colony and in the other colonies, in 1937. In Table 2 are recorded the days of fever in each group. From this table it appears possible that a certain amount of protection was afforded by the S–15 virus vaccine, even though the incidence of febrile respiratory infections in this group and in the unvaccinated group were approximately the same. Excellent protection against the epidemic disease appeared to be afforded by the PR–8 virus vaccine.

TABLE 1.—SUMMARY OF CLINICAL RESULTS—COLONY N.L., MARCH, 1936.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated . .	550	69	12.5	59	10.7
S–15 vaccinated .	138	17	12.4	20	14.3
PR–8 vaccinated .	110	3	2.7	16	14.5

Application of the X^2 test to these data shows that the observed differences in the febrile cases between the PR–8 vaccinated and the unvaccinated groups are significant.

TABLE 2.—DAYS OF FEVER: 89 CASES OF UPPER RESPIRATORY INFECTION, COLONY N.L., MARCH, 1936.

Group.	Vaccine.	Total days of fever.	Days fever per person.
A	Human	9	.08
B	Swine	39	.28
C	None	253	.46

Colonies N.L. and J. have had closer and more frequent contact with urban centers than the other four colonies. In their epidemics of 1937 the first cases of respiratory infections were among employees who had been visiting in such centers, and among boys who had been on vacation.† The epidemic of influenza as studied by Francis and Magill[2] in New York City had reached its height in the latter part of December, and a less severe influenza epidemic reached its

* Although the majority of the febrile respiratory infections were considered to be influenza at the time of occurrence, so few ferrets were then available that it was considered wiser to wait for a spread of the disease throughout the colony before obtaining nasopharyngeal washings. This spread did not occur.

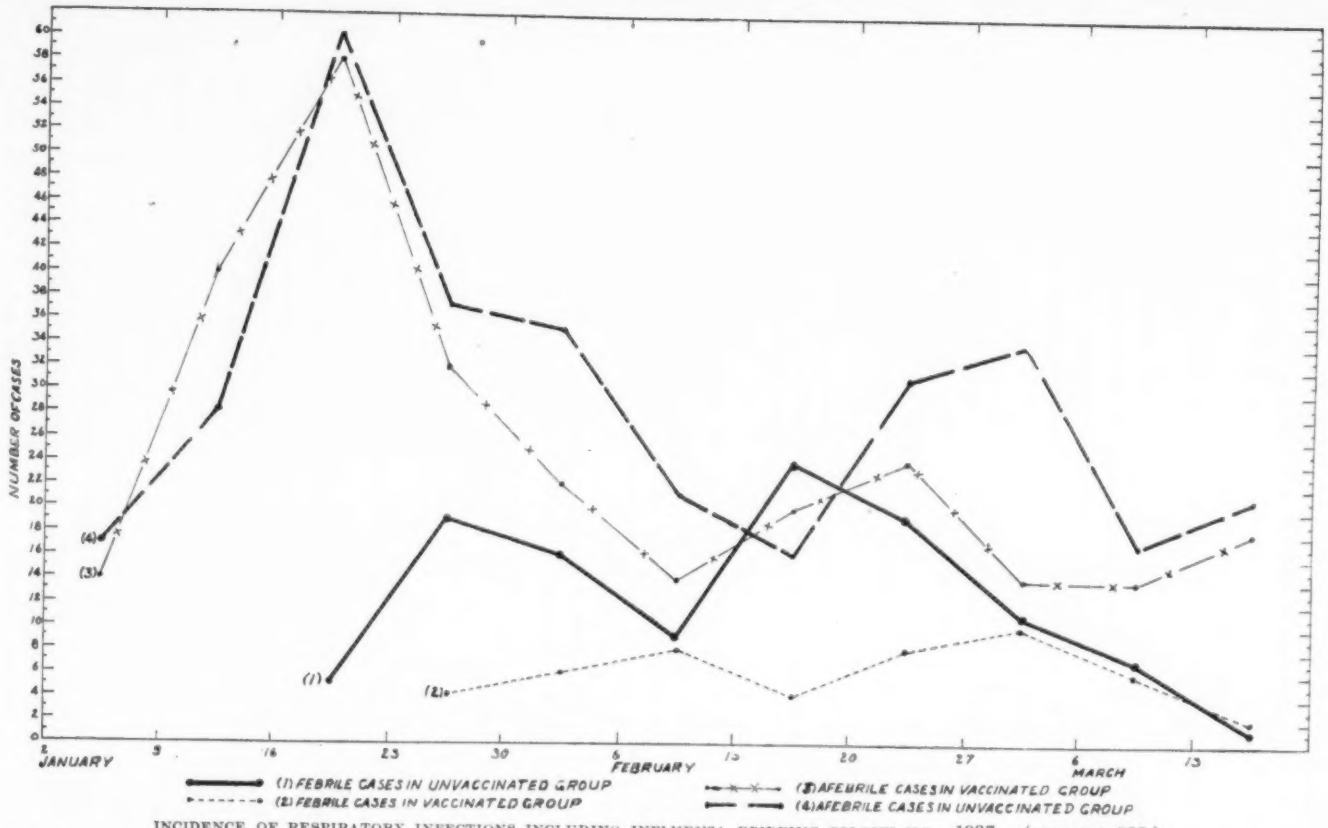
† Vacations are allowed from Colonies N.L. and J., but from none of the other institutions studied.

height in Philadelphia during the early part of January. In Colony N.L. the influenza epidemic began on about January 20, 1937, reaching its height through February, while in Colony J. a smaller epidemic started about February 1, 1937, and reached its height at approximately the same time. The three intramuscular injections at weekly intervals were completed in Colony N.L. on December 15, 1936, whereas they were completed in Colony J. on November 28, 1936. The signs, symptoms and course of the disease were characteristic of what was noted throughout most of the United States during this same period, with certain slight variations in the different colonies studied.

In Chart I is recorded graphically the course of the 1937 epidemic at Colony N.L. It will be noted that before and after the epidemic when only afebrile respiratory infections were occurring, there was little if any difference in incidence of infections between the vaccinated and unvaccinated groups. This equal incidence of afebrile respiratory infections in the vaccinated and unvaccinated groups among all the colonies when free of epidemics is striking evidence favoring the statistical value of differences in incidence of febrile infections between the two groups when the epidemics occurred.

Each peak of febrile infections in the unvaccinated group was closely followed by a peak of afebrile infections in the same group, without any corresponding peaks of infection in the vaccinated group. From this it would appear that afebrile respiratory infections which were actually mild influenza occurred while the incidence of febrile influenza was dropping toward the end of the epidemic, but that this sudden rise of mild influenza did not occur in the vaccinated group due possibly to the protection afforded by the vaccine. It is also interesting that at the height of the epidemic during the week when there were 25 febrile cases in the unvaccinated group, only 2 febrile cases occurred among the vaccinated group. After March 1st, the nature of the respiratory infections in the febrile cases markedly changed. At this time there was no longer the sudden onset with chill, generalized aches, and pains, followed by a racking cough, but rather a purulent type of infection involving the nose and throat practically free of cough in the early stages, but with a thick purulent discharge from the sinuses. It appeared possible that this was entirely of bacterial origin; a hypothesis partially confirmed by the fact that from nasopharyngeal washings taken at this time the human influenza virus could not be isolated.

Previously on February 2 and February 4 from all pools of nasopharyngeal washings taken from unvaccinated individuals, human influenza viruses had been isolated. The washings from one vaccinated individual were included in one of these pools without separation from the other washings, and it is therefore impossible to determine whether or not the human influenza virus was present in his secretions, as distinguished from the secretions of others in



INCIDENCE OF RESPIRATORY INFECTIONS INCLUDING INFLUENZA EPIDEMIC COLONY N.L., 1937. (INMATES–800.)

CHART 1.—Each point on the graphs represents the total number of cases for each week as shown on the abscissa. For proper comparison the 2 lines for the vaccinated group represent approximately twice the actual incidence of cases, since the unvaccinated group in the colony was approximately twice the size of the vaccinated group.

the same pool. Due to the alteration in the character of the febrile infections and to the inability to obtain human influenza virus during this same period, Table 3 includes all febrile respiratory cases from January 20 to March 1, at which time the incidence of febrile cases was rapidly decreasing. Table 4 gives a comparison of the number of days of fever in the two groups. In this colony the majority of the white blood cell counts during the epidemic were between 3000 and 6000, and while some were as high as 9000, very few fell above this figure. Of those with temperatures of 102° and over there were 36 individuals among the unvaccinated group and only 5 among the vaccinated group; an indication of the marked difference in severity between the groups. The marked difference in total days of fever in the two groups as shown in Table 3 also indicates the difference in severity. The majority of those with high temperatures in the vaccinated group, however, appeared to be typical cases of influenza with characteristic signs, symptoms, and a low white cell count.

TABLE 3.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY N.L., JANUARY 20 TO MARCH 1, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	525	95	18	176	33.5
Vaccinated	275	16	5.8	71	25.8

Application of the χ^2 test to these data shows that the observed differences in the febrile cases between the PR–8 vaccinated and the unvaccinated groups are significant.

TABLE 4.—COMPARISON OF DAYS OF FEVER AND HEIGHT OF FEVER IN TWO GROUPS, COLONY, N.L.

Group.	Total days.	Days per case.	Average per individual.	Cases with 102°–102.8°	Cases with 103° and over.
Unvaccinated	311	3.3	.59	22	14
Vaccinated	37	2.3	.13	2	3

Among the 107 inmates who had been vaccinated in March, 1936, with the human influenza virus (PR–8) and again in December, 1936, there were 4 with febrile respiratory infections occurring during the epidemic. The dates of their admission to the hospital were January 26, January 30, February 10, and February 22, 1937. Among the 133 inmates who had been vaccinated in March, 1936, with the S–15 virus, and again in December, 1936, with the PR–8 virus, there were 6 with febrile respiratory infections occurring during the epidemic. The dates of their admissions to the hospital were January 25, February 2, 18, 22, and 27. Among the 16 febrile cases who had been vaccinated, there were 6 who had received only one course of virus vaccine, *i. e.*, December, 1936.

Chart II graphically represents the smaller epidemic in Colony J. The same rise in incidence of the afebrile cases while the incidence of febrile cases was falling in the unvaccinated group is evident. Table 5 shows a comparison of the incidence of respiratory infec-

the 2 lines for the vaccinated group represent approximately twice the actual incidence of cases, since the unvaccinated group in the colony was approximately twice the size of the vaccinated group.

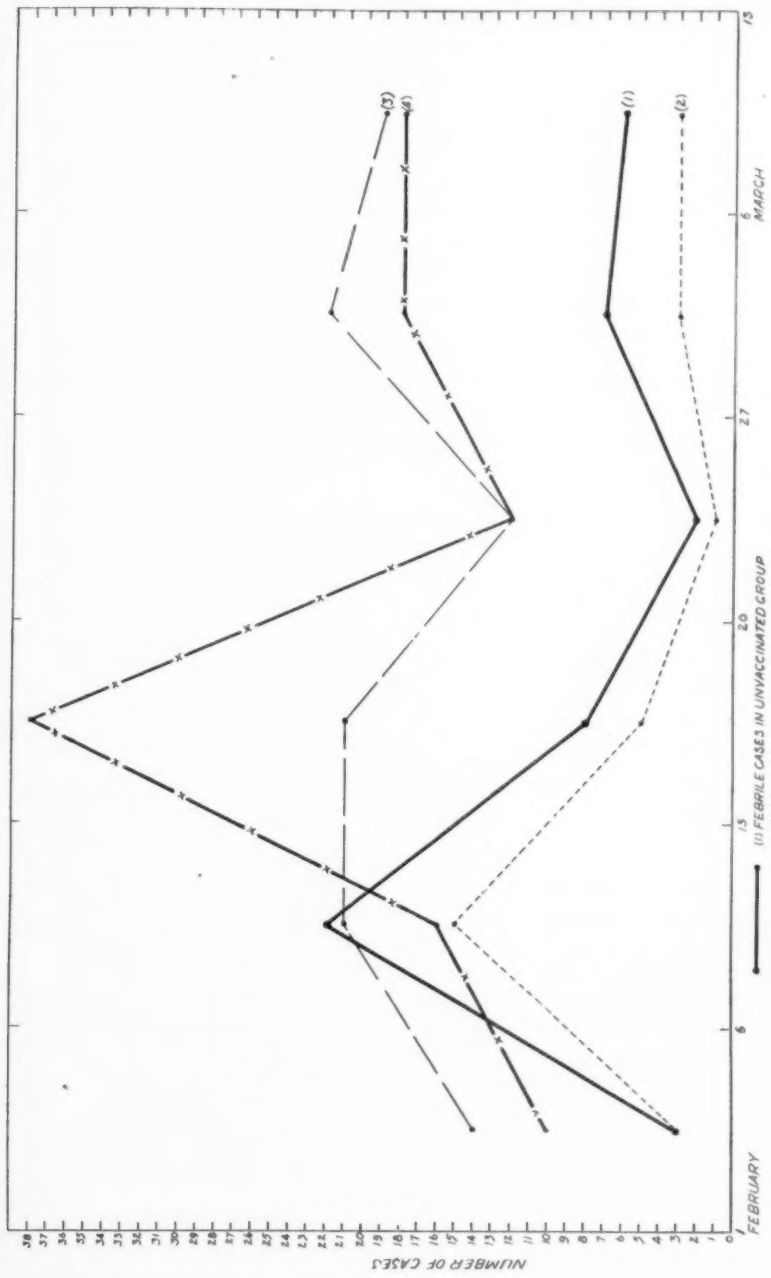

NUMBER OF CASES
FEBRUARY
MARCH
(1) FEBRILE CASES IN UNVACCINATED GROUP
(2) FEBRILE CASES IN VACCINATED GROUP
(3) AFEBRILE CASES IN VACCINATED GROUP
(4) AFEBRILE CASES IN UNVACCINATED GROUP

CHART II.—Each point on the graphs represents the total number of cases for each week as shown on the abscissa. For proper comparison the 2 lines for the vaccinated group represent approximately twice the actual incidence of cases, since the unvaccinated group in the colony was approximately twice the size of the vaccinated group.

INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY J., FEBRUARY–MARCH, 1937.

tions in this colony, while Table 6 gives a comparison of the days of fever and height of fever in the unvaccinated and vaccinated groups. On account of the small number involved, the difference in incidence between the two groups would not be highly significant were it not for the difference in the severity of infection in the two groups. Of those with temperatures of 102° and over there were 26 in the unvaccinated group and only 2 in the vaccinated group. On account of the diminishing supply of ferrets, nasopharyngeal washings were obtained from but one unvaccinated febrile boy (W. M.), and from one vaccinated febrile boy (H. N.), on February 13, 1937. A virus identified as similar to PR–8 was isolated by ferret and mouse passage from the washings of the vaccinated boy. In this epidemic the white cell counts were high for influenza, the large majority being 9000 or above. The obvious possibility, therefore, that secondarily invading bacteria played an important part in this epidemic, must be considered. However, the signs, symptoms and course of the disease in most instances were characteristic of mild epidemic influenza.

TABLE 5.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY J., FEBRUARY 1 TO MARCH 13, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	357	42	11.8	107	30
Vaccinated	193	13	6.7	57	29.5

TABLE 6.—COMPARISON OF DAYS OF FEVER AND HEIGHT OF FEVER IN TWO GROUPS, COLONY J.

Group.	Total days.	Days per case.	Average per individual.	Cases with 102°–102.8°.	Cases with 103° and over.
Unvaccinated	112	2.66	.31	19	7
Vaccinated	36	2.77	.19	2	0

TABLE 7.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY S., FEBRUARY 20 TO APRIL 15, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	970	42	4.3	88	9.1
Vaccinated	480	9	1.9	32	6.7

In Colony S. approximately 1450, of whom about one-third were vaccinated, respiratory infections resembling epidemic influenza were limited to a few of the cottages. In Table 7 is recorded the incidence of respiratory infections in this colony from February 20 to April 15, 1937. The first 3 vaccine injections were completed on December 6, 1936, and an additional injection was given on March 14, 1937, since at that time a more rapid spread of the disease was expected from the few cottages already affected. This rapid spread did not occur; but it is of interest that after March 14, 18 febrile respiratory infections occurred in the unvaccinated group and only 2 extremely mild febrile infections occurred in the

vaccinated group. Previous to this period, from February 20, to March 14, 1937, the comparative incidence in same order was 24 to 7. The incidence of afebrile respiratory infections in the two groups during other parts of the year was practically the same, for which reason the difference found during this period of febrile infections would appear to be significant.

A large number of the white cell counts were low, but there were many counts of 10,000 and over. Nasopharyngeal washings were not injected into ferrests chiefly on account of the scarcity of these animals, and for the other reasons mentioned. Probably due to the fact that this colony is more strictly isolated than the others the febrile respiratory infections did not occur until late winter and early spring.

Discussion. The simplest explanation of the results recorded is that man, like other susceptible animals, develops immunity by intramuscular injections of active human influenza virus, the degree of immunity varying inversely with the length of time following vaccination as demonstrated by exposure to the disease. Although obviously the large number of other factors involved do not permit of simple explanations, certain of the data to be mentioned fulfill the requirements of such a hypothesis.

If the epidemic of March, 1936, at Colony N.L. was due chiefly to the human influenza virus, which appears probable, the most solid immunity was afforded when the active human virus was injected intramuscularly in advance of the oncoming epidemic. However, the number in the group vaccinated with human virus was not large (110) nor is it clear why the swine virus (S–15) vaccine appeared to reduce the number of days of fever only and did not reduce the incidence of respiratory infections. It is possible that antigenic differences in the two strains of virus may account for the different responses of suceptible individuals, and that the findings of Magill and Francis[3] are applicable primarily to the rabbit or other naturally immune animals. In addition, filtering the mouse-lung vaccine emulsion through Berkefeld filters reduced considerably the potency of the vaccine. More potent swine influenza virus vaccine might have produced a better cross immunity against the human virus disease.

Next in order of efficacy appeared to be the intramuscular vaccinations of the same Colony N.L. ending on December 15, 1936, 36 days before the onset of the influenza epidemic on January 20, 1937, from which the human virus was obtained by passage in ferrets. The marked reduction in incidence of febrile respiratory infections and particularly in days of fever in the vaccinated group rather closely approached the favorable results obtained one year earlier; also the larger number included in the group vaccinated with human virus (275) added to the statistical value of the data. However, in a comparison of these results with others, it must be remembered that most of those included in the vaccinated group

had received either human or swine virus in mouse-lung emulsions intramuscularly in March, 1936, which may have assisted the immunity developed by the more recent vaccination.

In the very small epidemics of Colonies J. and S. is to be noted the least efficacy of the vaccine in protecting those injected and at the same time the longest interval between vaccination and the onsets of the epidemics, namely, 64 days in Colony J. and 76 days in Colony S. Confusing factors in Colony J. were the finding of human influenza virus in nasopharyngeal washings from a vaccinated individual and the generally higher white cell counts of around 9000, an unusual finding for epidemic influenza. For these reasons question has arisen as to whether a different strain of influenza virus was present in Colony J., despite the fact that cross neutralization was obtained with human influenza virus PR–8, and also as to whether bacterial factors played an important or possibly a primary rôle in the epidemic. However, the marked reduction in the height of fever—26 individuals with temperatures of 102° and over in the unvaccinated group as compared to 2 individuals in the vaccinated group—and the moderate reduction in incidence in the vaccinated group as compared to the unvaccinated group suggest that the human influenza virus as a causative agent and the protection afforded by its injection were important factors in these febrile respiratory infections.

However, in all of the epidemics of febrile respiratory infections here recorded, the possibility that bacteria may have been important factors, must be considered. In Colony S. the fact that following an additional injection of vaccine on March 14, 1937, 18 febrile respiratory infections occurred in the unvaccinated group up to April 15, 1937, and but 2 in the vaccinated group from the standpoint of immunity would appear also to favor the importance of a short interval between vaccination and the onset of an epidemic. From March 14 to April 8 no febrile respiratory case occurred among the vaccinated group. However, the comparatively small number of febrile cases in the unvaccinated group lessens the statistical value of this finding.

On the single attempt made, human influenza virus was found in Philadelphia in nasopharyngeal washings from a nurse with typical epidemic influenza. The strains of virus isolated from the different colonies and from Philadelphia, are being studied and the findings concerning them will be reported later. All of the strains showed cross-neutralization with the PR–8 strain of human influenza virus.

In the other 3 colonies vaccinated, V.T., VS. and W., and among a Philadelphia nursing group (120) of whom one-half were vaccinated, there were no significant findings since respiratory infections at no time reached epidemic proportions.

Referring to the simple hypothesis mentioned above, it would appear, therefore, that a considerable degree of immunity to epi-

demic influenza can be produced by intramuscular injections of active human influenza virus, but it is not clear as to whether such immunity is of short or long duration.

Summary. 1. Human beings in 5 large State Colonies and in one private institution were vaccinated intramuscularly with active virus (PR–8) of human influenza, covering the epidemics of respiratory infections of two winters, 1935–1936 and 1936–1937.

2. The method of vaccination is discussed. Approximately one-third of the inmates of each institution was vaccinated. No generalized or marked local reactions occurred from the chick embryo virus cultures used, and there was no evidence of the vaccinations causing any respiratory infections. This was readily determined as the vaccinations were performed at a time when practically no respiratory infections were present in any of the institutions studied.

3. Several epidemics of influenza in Philadelphia and among the institutions are described, from 3 of which human influenza viruses were obtained. All of these viruses showed cross-neutralization with strain PR–8 of human influenza virus.

4. The protection afforded by vaccination with active human influenza virus and the possible importance of the interval between vaccination and the onset of the epidemic, are discussed.

We wish to acknowledge the aid of Drs. Ralph G. Gladen, New Lisbon, N. J.; Matthew Molitch, Jamesburg, N. J.; Dan S. Renner, Skillman, N. J.; Rayford K. Adams, Skillman, N. J.; Margaret E. Shirlock, Vineland, N. J. and Edwin H. Van Deusen, Vineland, N. J.

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VASOCONSTRICTOR PROPERTIES OF BENZEDRINE AND ITS USE IN THE RELIEF OF THE COMMON COLD.

By Eldon M. Boyd, M.A., M.D., C.M.,
assistant professor of pharmacology, queen's university,
and
W. Ford Connell, M.D., C.M., M.R.C.P. (Lond.),
associate professor of medicine, queen's university,
kingston, ontario, canada.

A number of papers have appeared describing the use of benzedrine in the treatment of the common cold. It is the purpose of the present communication to present a critical study of 59 additional cases and to present pharmacologic evidence regarding the vasoconstrictor properties of this substance.

Bertolet[2] reported that practically 9 out of 10 cases with nasal congestion obtained some relief from the use of benzedrine, the result being excellent in one-quarter of his patients. This result was confirmed by Byrne[4] who noted in addition that it was of no value in patients with an underlying sinusitis. Scarano[9a] found benzedrine and ephedrine about equally efficacious in relieving nasal congestion which was confirmed by Giordano;[6] Scarano[9b] in a later paper presented drawings clearly illustrating the shrinkage effected by benzedrine. Sulman[10] stated in addition that benzedrine not only controlled congestion but he believed it caused abortion of colds and prevented the occurrence of further colds in susceptible patients.

Benzedrine (benzyl-methyl-carbinamine or β-phenylisopropyl-amine), a volatile synthetic sympathomimetic substance more closely allied structurally to ephedrine than to epinephrine, was studied by Pines, Miller and Alles[8] in 1931. Benzedrine is less closely related structurally and pharmacologically to epinephrine than the new synthetic substance meta-synephrin or neo-synephrin.[3]

Clinical Study. Benzedrine* was dispensed as an inhaler to over 200 students at the University Clinic upon whom a diagnosis had been made of acute or vasomotor rhinitis. Each student was instructed to inhale once through each nostril not more frequently than every hour. Records were kept separately of the average number of colds per year, their average duration and usual treatment, the effect of benzedrine upon the symptoms and duration of the cold so treated and other relevant data. Some of the students failed to report the results and data in other cases had to be excluded because they were incomplete or unreliable.

Of 59 cases with satisfactory data, only 3 reported no relief whatsoever of symptoms; 16 recorded the result as fair, 27 as good and 13 as excellent. These figures appear to confirm the efficacy of the substance, but there remained a suspicion that many of the students who failed to report again did so because the treatment had not been beneficial. Whether or not this be true, the results are in agreement with those previously recorded and indicates that benzedrine is of considerable value in relieving nasal congestion.

Each of the patients treated suffered from an average of approximately 4 colds per year and each cold lasted an average of about 9 days. In contrast, 27 further students who stated that they were relatively free of colds had an average of 2 colds per year lasting 4 days each. The group under treatment was thus definitely susceptible to colds. While benzedrine was efficient in relieving nasal congestion, it had practically no effect on the average duration of the colds. In the treated group, previous colds had lasted a mean of 8.7 days each, while the average duration of the cold treated with benzedrine was 8.1 days.

* Benzedrine inhalers and benzedrine sulphate used in the present investigation were supplied to us by the Smith, Kline & French Laboratories of Philadelphia, and ephedrine hydrochloride used for comparative purposes by the Abbott Laboratories of Montreal.

The Toxicity of Benzedrine Sulphate to Mucosal Surfaces. The toxicity of benzedrine has been studied by Hartung and Munch,[7] Ehrich and Krumbhaar,[5] and Alles[1] who determined the minimum lethal dose in rats and guinea pigs. There is no experimental evidence regarding the toxicity or relative toxicity of benzedrine toward mucosal surfaces which was the information more particularly required in the present study. This was obtained by comparing the relative effects of benzedrine, ephedrine and epinephrine on the activity of cilia in the mucosa lining the esophagus of the frog. Pithed frogs were pinned on their backs, the lower jaw removed, the esophagus split, the mucosa gently washed with saline and a light mustard seed allowed to be carried by the cilia over a measured distance of the ciliated surface. The length of time in seconds required for this was determined repeatedly until consistent readings were obtained and then the mucosa was gently washed with 0.1% benzedrine sulphate or 0.1% ephedrine hydrochloride or 0.1% epinephrine hydrochloride and the process repeated. Two dozen frogs were used to determine the effect of each drug.

TABLE 1.—THE EFFECT OF BENZEDRINE, EPHEDRINE AND EPINEPHRINE UPON THE NUMBER OF SECONDS REQUIRED BY CILIA IN THE ESOPHAGEAL MUCOSA OF THE FROG TO CARRY A SEED A GIVEN DISTANCE.

	Solution applied (0.1%).								
	Benzedrine.			Ephedrine.			Epinephrine.		
Value.	Before.	After.	Difference.	Before.	After.	Difference.	Before.	After.	Difference.
Minimum* . .	13	19	− 6	12	14	−20	18	20	−25
Maximum* .	80	125	+94	60	100	+50	75	115	+50
Mean . . .	34	52	+18	34	43	+10	40	43	+ 3
Standard deviation . . .	14	24	21	12	21	15	16	29	22

* The minimum and maximum values are for each column and hence the "difference" values do not necessarily represent the difference between the preceding values in the line.

The results obtained have been depicted in Table 1. The values given include the shortest interval required to carry the mustard seed the given distance, the longest interval, the mean interval and the standard deviation of the mean. In 18 of 22 frogs (82%) application of 0.1% benzedrine sulphate produced slowing of ciliary motion, the rate being on the average 65% of that previous to the application of the drug. On the other hand, similar concentrations of ephedrine hydrochloride and epinephrine hydrochloride had no consistent effects upon ciliary motion. On the average, the rate was slightly slower with each of the latter drugs but in both instances there were just about as many frogs which exhibited increased as decreased rates. It may be concluded that benzedrine sulphate is slightly more toxic to ciliary motion than ephedrine or epinephrine hydrochlorides.

The Vasoconstrictor Properties of Benzedrine Sulphate. Experiments were performed in an effort to ascertain the site at which benzedrine produces vasoconstriction and also to compare its power of vasoconstriction with that of ephedrine and epinephrine. One-

half cc. of 0.01% of the respective salts of each of these substances was injected into the peripheral circulation of frogs perfused with Ringer's solution in the usual manner. In 12 of 15 frogs, benzedrine sulphate caused the rate of flow of the perfusate to diminish, the average maximum constriction produced in each frog being 34%. A similar dose of ephedrine hydrochloride had practically the same effect, the average maximum constriction being 31%. Epinephrine produced constriction in all experiments and the average maximum constriction was 49%. Benzedrine is thus about as efficient as ephedrine but less so than epinephrine in its vasoconstriction of the peripheral vessels of the frog.

When the same dose of epinephrine hydrochloride was introduced into ergotaminized frogs, vasodilatation occurred in 9 out of 10 animals, the average maximal increase in the rate of flow of the perfusate being 105%. Under the same conditions, benzedrine sulphate produced an increase of 114%. Hence it may be concluded that benzedrine acts upon the motor sympathetic endings in the blood-vessels of the frog. From experiments upon cocainized frogs it was found that the mechanism of this action is not the same as that of epinephrine. A dose of 0.5 cc. of 0.01% epinephrine hydrochloride produced an average maximum constriction of 79% in cocainized frogs, cocaine sensitization being evidenced by all of the animals. But cocaine had no effect on the vasoconstrictor properties of benzedrine sulphate.

Benzedrine was less efficient than epinephrine and about equal to ephedrine in raising the blood pressure of rabbits anesthetized with urethane and ether. Eight animals were used and a dose of 1 cc. of 0.005% of the respective salts was injected intravenously on repeated occasions. The average maximal increase in blood pressure with epinephrine was 160%, with ephedrine 77% and with benzedrine 71%. The average blood pressure before injecting epinephrine was 50 mm. of mercury and after it the average maximum blood pressure was 130; before ephedrine the average was 48 mm. and after, 85; before benzedrine the average was 38 and after, 65. The average duration of the complete effect of epinephrine was 159 seconds, of ephedrine 91 seconds and of benzedrine 71 seconds. The effect of benzedrine was not as consistent as that of either of the other two substances; the first dose given an animal usually produced a well-marked rise in blood pressure but subsequent doses usually had less effect.

Previous cocainization enhanced the effect of epinephrine on the blood pressure of rabbits, but actually decreased the response to ephedrine and benzedrine. From 10 experiments with each drug, epinephrine immediately after cocainization produced a mean maximal increase in blood pressure of 203%, ephedrine of 3.5% and benzedrine of 17%. In a number of instances a fall in blood pressure occurred on injecting ephedrine or benzedrine after cocaine. Previous ergotaminization diminished but did not reverse the effect

of ephedrine and benzedrine; the average maximum rise in blood pressure produced by the same dose of benzedrine sulphate in 7 ergotaminized rabbits was 17% and of ephedrine hydrochloride 10%. Hence benzedrine, like ephedrine, acts on the motor sympathetic endings in rabbit vessels but not in a manner identical to that of epinephrine and in addition it must act to a certain extent directly on the muscle since some constriction occurred in ergotaminized animals.

Conclusions. 1. From clinical studies on the topical application of benzedrine in the relief of the common cold, it appears that benzedrine relieves symptoms resulting from nasal turgescence but does not shorten the duration of the cold. Water soluble benzedrine sulphate is more toxic to the mucosa than either ephedrine or epinephrine though not greatly so.

2. From pharmacologic studies on frogs and rabbits, it appears that benzedrine acts by stimulation of the motor sympathetic endings in the vessel wall but not in the same manner as epinephrine and in addition probably acts to a certain extent directly upon the smooth muscle. In this vasoconstrictor property it is about as efficacious as ephedrine but less so than epinephrine.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

II. Production of Acute Exacerbation of Toxemia by Sodium Salts in Pregnant Women with Hypoproteinemia.*

By Maurice B. Strauss, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.)

The designation "toxemia of pregnancy" has included at one time or another almost all the non-septic, non-mechanical ills of the gravid state. At the present time certain of these conditions, such as the

* Aided by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

anemias[7] and the polyneuritis[8] of pregnancy, are regarded as due to nutritional deficiency. It has also become apparent that the diagnosis "toxemia of pregnancy" has in the past included such conditions as essential hypertension, acute and chronic glomerulonephritis, pyelonephritis, and rarely malignant nephrosclerosis. In fact, probably five-sixths of patients said to have "toxemia" of pregnancy are suffering from some independent and frequently pre-existing disease in which the pregnancy is merely an incident. Nevertheless there remains a group of patients who have been apparently well prior to pregnancy and who exhibit no evident abnormalities after the puerperium, but who do develop relatively acute arterial hypertension in the last trimester of pregnancy, and who do not exhibit the clinical or laboratory findings of glomerulonephritis, pyelonephritis, or malignant nephrosclerosis. These patients have been shown to have markedly diminished plasma proteins invariably associated with water retention.[6a,b] The condition has usually been designated "low reserve kidney," "pre-eclampsia," or "eclampsia," depending on the severity of the condition.[5] Lastly there are patients with pre-existing arterial or renal disease in whom the development of increasing hypertension or albuminuria is associated with hypoproteinemia and water retention.

The studies to be reported here indicate that hypoproteinemia is the primary factor permitting significant water retention in pregnancy and that such retention may be accompanied by considerable rises in blood pressure, increasing albuminuria and the appearance of such pre-eclamptic manifestations as severe headache, visual disturbances, and vertigo. It is known that the administration of sodium salts to normal individuals may produce slight increments of water retention, whereas in individuals with lowered plasma proteins marked retention may occur in inverse proportion to the plasma protein level.[4] There is evidence that the bicarbonate is more effective than the chloride of sodium in inducing water retention.[4] The mechanism by which sodium salts produce water retention is a complicated one. For a thorough discussion of this problem Peters' "Body Water"[3] may be consulted.

Methods. Women in the last trimester of pregnancy were admitted to the Thorndike Ward of the Boston City Hospital, but *not* put to bed. Each patient received the usual ward diet. Fluids were allowed *ad libitum*. The patients were not encouraged either to increase or decrease their fluid intake. Each patient was weighed upon arising in the morning. About 2 hours after breakfast, the patient having been in a chair for at least 20 minutes, the blood pressure was measured. The daily fluid intake and output were recorded. On the morning after admission to the hospital and at intervals thereafter 20 cc. of blood were withdrawn without stasis from an antecubital vein for analysis. The patients were recumbent for ½ hour prior to this procedure. The 24-hour urine was analyzed daily for albumin by the quantitative method of Tsuchiya. The total plasma protein and the plasma albumin were determined by a micromodification of Howe's method.[2] In the tables, the "initial" blood pressure represents the *average* of the first

3 days' readings. The change in blood pressure recorded represents the difference between this average and the *average* of the three readings obtained on the mornings of the last 2 days of the test period and that of the morning after the test period. The "initial" weight represents the reading on the day the test period began. The change in weight represents the difference between this weight and that recorded on the first morning after the test period.

TABLE 1.—RESPONSE TO THE ADMINISTRATION OF SODIUM SALTS FOR 7 DAYS IN 8 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES ABOVE 220 MM. H_2O.

Case No.	Weight gain.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
		mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H_2O.
	%	Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
1	0	−6	−19	154	70	125	74	0	2597	2057	230
2	0	−3	0	145	90	138	83	0	2622	1630	255
3	0.8	+3	+ 2	170	96	130	77	0	1440	1514	250
4	1.2	+1	+19	184	118	124	87	0	3030	3026	248
5	1.4	−4	−11	146	90	119	86	0	2391	1093	260
6	1.6	+1	−18	220	110	198	100	0	3214	1855	225
7	1.8	−2	− 2	184	118	139	91	0	2468	3063	230
8	1.8	+1	0	150	100	135	85	0	2760	1470	252
Av.	1.1	−1	− 3	169	99	138	85	0	2565	1963	244

Case 6 received sodium bicarbonate.

Observations. I. Eight women known to have had some degree of arterial hypertension either before or early in pregnancy were studied in the last trimester of pregnancy. The osmotic pressure of the plasma proteins, calculated by the method of Wells, Youmans and Miller, varied from 230 to 260 mm. of water (Table 1). None of these women had significant albuminuria. In practically every instance the initial average blood pressures recorded in the table are lower than those recorded prior to admission to the hospital. Why hospitalization without bed rest should result in a fall in blood pressure is not for discussion here.

On the third morning of their hospital stay 7 of these women commenced receiving 16 gm. of sodium chloride (= 6.3 gm. of Na) daily, and one (Case 6) commenced taking 23 gm. of sodium bicarbonate (= 6.3 gm. of Na) daily for a minimum period of one week. Gains of weight up to 1.8% of the initial body weight were observed (Table 1). None developed visible edema. No significant changes in diastolic blood pressure occurred (Table 1). In no instance did albuminuria increase nor did cylindruria or hematuria appear. No subjective symptoms occurred. Observations in two typical cases are charted (Charts I and II).

It thus appears that the daily administration of 6.3 gm. of sodium (either in the form of 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate) results in small increments of weight, but is without other

effect on women with arterial hypertension in the last trimester of pregnancy who have essentially normal plasma protein values.

TABLE 2.—RESPONSE TO THE ADMINISTRATION OF SODIUM SALTS FOR 7 DAYS IN 10 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES BELOW 220 MM. H_2O.

Case No.	Weight gain.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
	%	mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H_2O.
		Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
11	{2.5	− 1	−10	125	85	123	78	0	2648	2052	172-207}
	{3.4	+ 6	+15	135	86	125	89	0	3034	2633	217-209}
12	3.3	+16	+14	182	108	133	79	0	2091	2090	200
13	3.6	+ 5	+ 3	184	106	147	81	0	4160	3820	212
14	4.7	+27	+31	142	84	131	82	+	2391	2585	192
15	4.8	+24	+30	154	100	136	90	0	3906	2320	210
16	5.5	+33	+11	162	100	135	80	+	6266	6253	193*
17	5.7	+12	+16	170	120	135	100	+	1920	1593	182*
18	5.9	+16	+ 7	165	90	128	75	0	2668	1335	180
19	7.2	+ 9	+ 7	156	100	144	92	+	3060	947	212
20	7.7	+ 6	+17	144	100	135	108	+	4185	2250	120*
Av.	4.9	+14	+14	156	98	134	86		3329	2524	192

* The test period was limited to 4 days or less in Cases 16, 17, 20 because of the development of pre-eclamptic symptoms.

The test period in Case 15 was limited to 5 days because of severe headache.

Cases 11, 14, 18, 19 received sodium bicarbonate; Cases 11 had 3 test periods (Chart IX); Case 12 had arterial hypertension prior to the pregnancy; Case 13 had chronic nephritis prior to the pregnancy.

TABLE 3.—RESPONSE TO THE FEEDING OF A HIGH PROTEIN DIET TO 6 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES BELOW 220 MM. H_2O.

Case No.	Weight loss.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
	%	mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H_2O.
		Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
31	2.9	−2	− 9	160	108	148	90	0	2562	1935	206
32	3.4	−5	−19	150	102	128	85	0	2371	1250	205
33	3.4	+3	− 3	170	110	143	87	0	3002	2735	218
34	3.7	−9	− 9	168	104	143	95	0	2334	2281	220
35	3.8	−5	− 8	160	120	136	100	0	2540	2544	210
36	4.1	−6	− 8	166	100	157	96	0	2880	2985	204
Av.	3.5	−4	− 8	162	107	142	92	0	2614	2288	210

II. Ten women were studied in the last trimester of pregnancy. All of them had some degree of arterial hypertension and 8 were known to have had normal blood pressures before or early in pregnancy. One patient had definite evidence of having essential hypertension and another chronic glomerulo- or pyelonephritis prior to pregnancy. The osmotic pressure of the plasma proteins, calculated as above, varied from 120 to 217 mm. of water. Five

patients showed albuminuria of from 0.3 to 2.8 gm. per liter. None had hematuria. On the third morning of their hospital stay 6 commenced receiving 16 gm. of sodium chloride (= 6.3 gm. of Na)

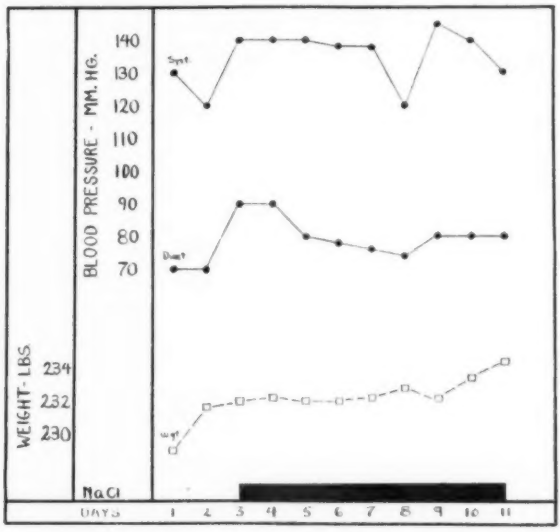

CHART I.—Weight and blood pressure changes in Case 3. Plasma oncotic pressure 250 mm. H_2O. Sodium chloride 16 gm. daily (solid block).

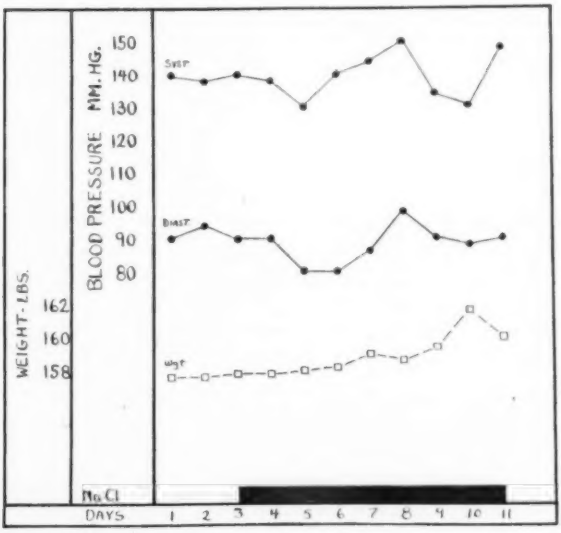

CHART II.—Case 7. Plasma oncotic pressure 230 mm. H_2O. Sodium chloride 16 gm daily (solid block).

and 4 commenced taking 23 gm. of sodium bicarbonate (= 6.3 gm. of Na) daily. Gains in weight of from 2.5 to 7.7% of the initial weight occurred, associated in each instance with the appearance of

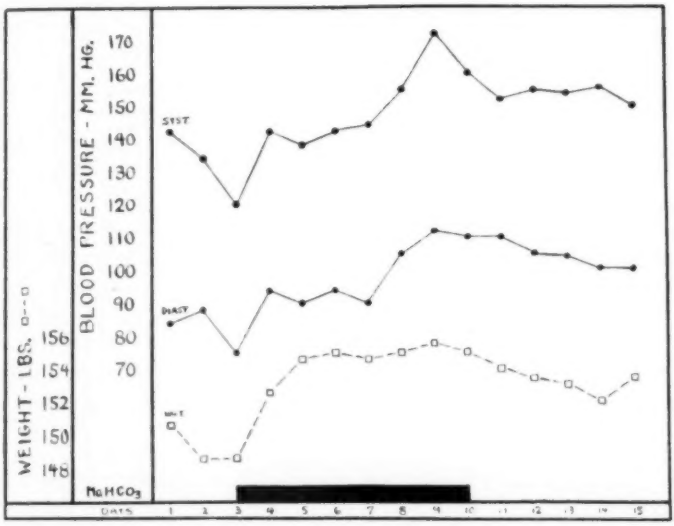

CHART III.—Case 14. Plasma oncotic pressure 192 mm. H_2O. Sodium bicarbonate 23 gm. daily (solid block).

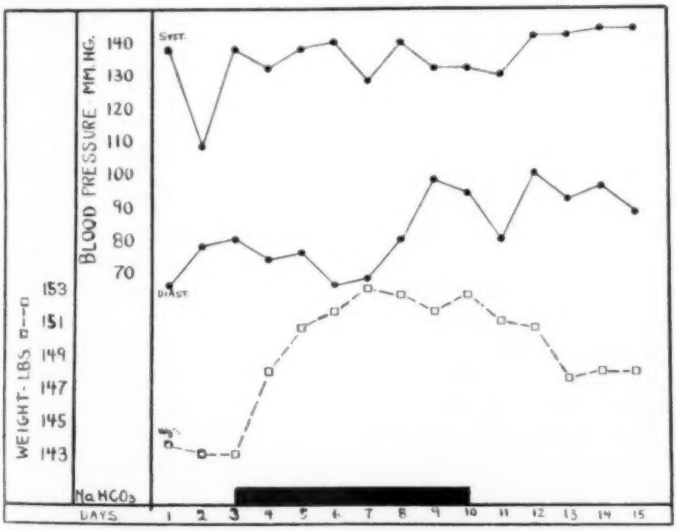

CHART IV.—Case 18. Plasma oncotic pressure 180 mm. H_2O. Sodium bicarbonate 23 gm. daily (solid block).

visible edema involving the extremities and frequently the face. Nine of the 10 women showed an elevation of arterial blood pressure, the diastolic being more consistently affected (Table 2) (Charts III to IX). Five showed significant increases in albuminuria so that the albumin varied from 1 to 5 gm. per liter. Cylindruria occurred in 2 patients and microscopic hematuria in one. In 2 patients the development of severe headache, visual disturbances, and vertigo necessitated the omission of sodium after 3 days (Charts VI and VII). A third patient was so uncomfortable from severe headache and edema that therapy was omitted on the fourth day (Chart VIII), and in a fourth, severe headache necessitated the omission of sodium after 5 days (Chart V).

It is thus apparent that the daily administration of 6.3 gm. of sodium (either in the form of 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate) results in significant gains of weight together with the appearance of visible edema in women with hypoproteinemia during the last trimester of pregnancy. In these women significant rises of arterial blood pressure occurred. In 5 albuminuria increased, and in 3 symptoms of pre-eclampsia appeared necessitating immediate cessation of the sodium administration.

One patient, Case 11 (Chart IX), had 3 test periods. During the first period, when her calculated oncotic pressure was 172 mm. of water, she received 16 gm. of sodium chloride daily for 9 days. Her weight increased slowly by 2.5%. The blood pressure was unchanged. During the next 6 days she received 23 gm. of sodium bicarbonate daily. Her weight increased slowly by an additional 1.5%. No change in blood pressure occurred. At the end of this period her plasma proteins had risen so that the calculated oncotic pressure was 207 mm. of water. One month later she was readmitted to the hospital with plasma proteins giving a calculated oncotic pressure of 217 mm. of water. At this time she was given 23 gm. of sodium bicarbonate daily. Her weight increased by 3.4% in 2 days, edema appeared, and her blood pressure rose from an average of 125 systolic and 89 diastolic to 140 systolic and 95 diastolic (Chart IX). However, during the continued administration of sodium her weight declined to its original level, edema disappeared, and concomitant with this her blood pressure fell to an average of 126 systolic and 74 diastolic.

This phenomenon of spontaneous diuresis and loss of edema during the continuous administration of sodium salts has been observed in patients with hypoproteinemia due to malnutrition or nephrosis and in animals subjected to plasmapheresis as well as those with nutritional hypoproteinemia.[1] No satisfactory explanation for this has been suggested.

III. Five patients of Group II were given ammonium chloride daily. One (Case 16) received 16 gm. daily 4 days after the omission of sodium chloride (Chart VI) for a period of 4 days during which

time she lost 3.5% of her body weight and her blood pressure fell from an average of 146 systolic and 103 diastolic to 125 systolic and 70 diastolic.

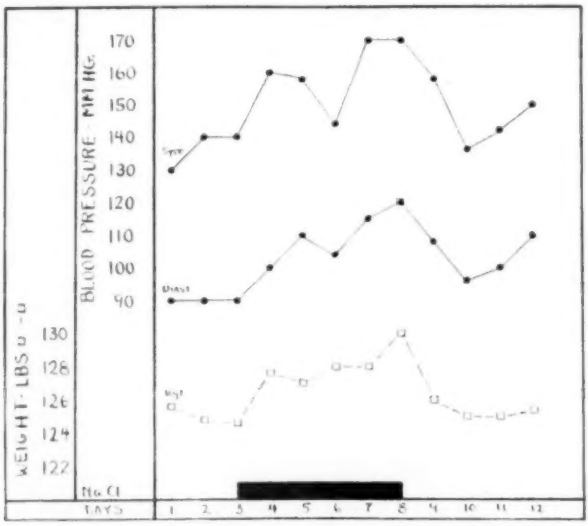

CHART V.—Case 15. Plasma oncotic pressure 210 mm. H_2O. Sodium chloride 16 gm. daily (solid block).

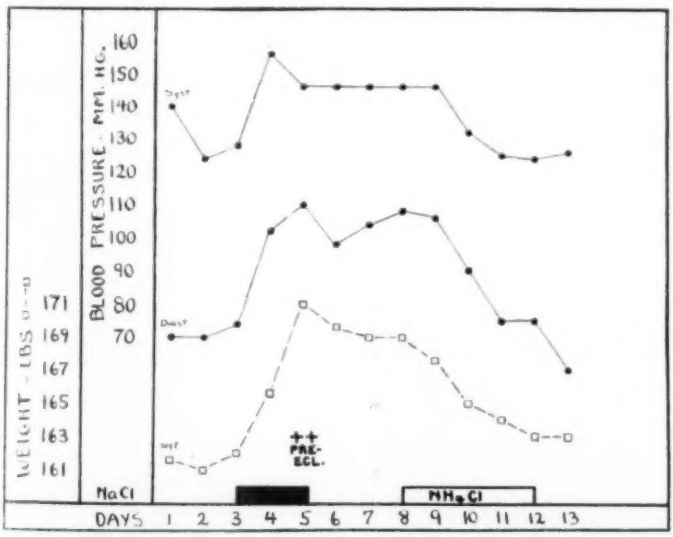

CHART VI.—Case 16. Plasma oncotic pressure 193 mm. H_2O. Sodium chloride 16 gm. daily for 2½ days (solid block). Ammonium chloride 16 gm. daily for 4 days (open block).

The second patient (Case 17) received 16 gm. of ammonium chloride daily for 6 days, 3 days after admission to the hospital

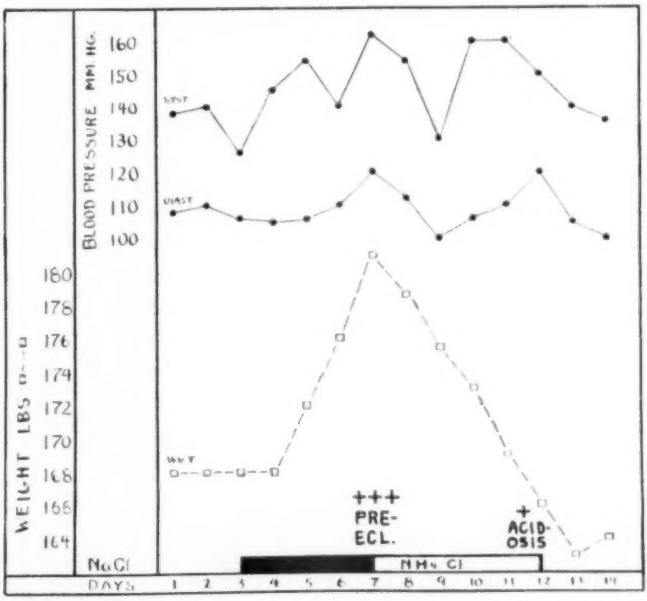

CHART VII.—Case 20. Plasma oncotic pressure 120 mm. H_2O. Sodium chloride 16 gm. daily for 4 days (solid block). Ammonium chloride 8 gm. daily for 5 days (open block).

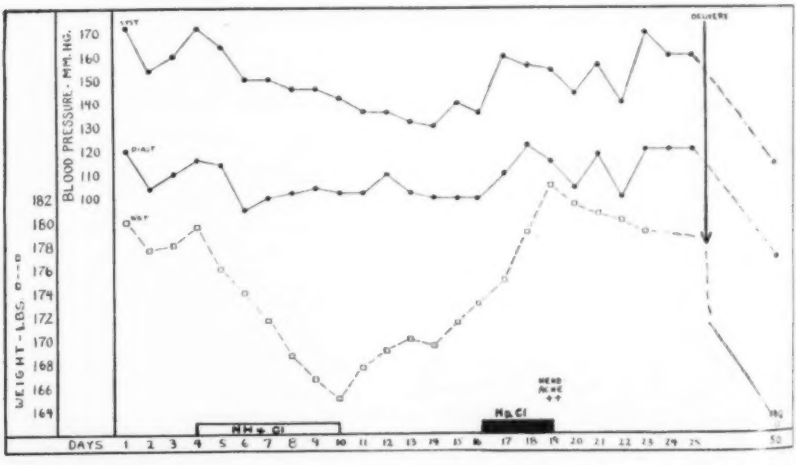

CHART VIII.—Case 17. Plasma oncotic pressure 182 mm. H_2O. Ammonium chloride 16 gm. daily for 6 days (open block). Sodium chloride 16 gm. daily for 3 days (solid block).

(Chart VIII). Her weight dropped by 8.1% in 6 days and her blood pressure fell from an average of 166 systolic and 110 diastolic to 144 systolic and 102 diastolic.

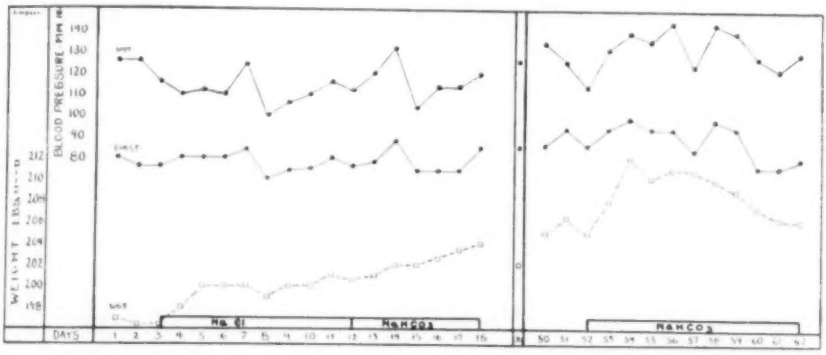

CHART IX.—Case 11. Plasma oncotic pressure 172 to 217 mm. H_2O. Sodium chloride 16 gm. daily for 9 days. Sodium bicarbonate 23 gm. daily for 6 and 10 days in second and third periods.

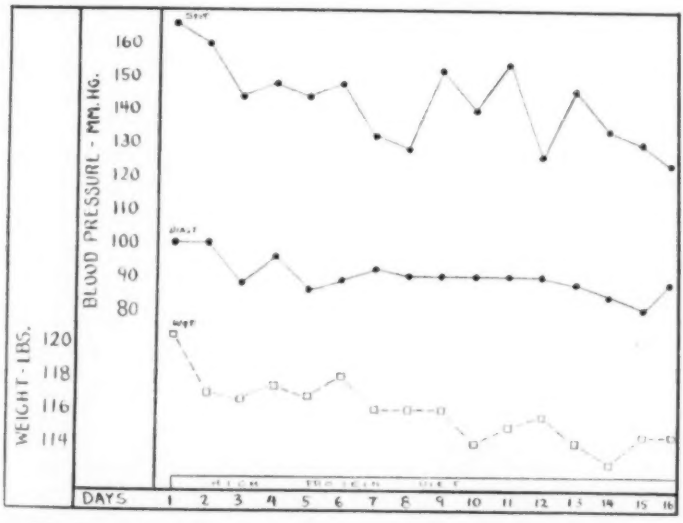

CHART X.—Case 36. Plasma oncotic pressure 204 mm. H_2O. 260 gm. protein diet for 16 days.

The third patient (Case 20) received 8 gm. of ammonium chloride daily immediately after pre-eclamptic symptoms had been produced by sodium chloride (Chart VII). Acidosis occurred after 4 days with hyperpnea, dyspnea, dehydration, and nausea. Her weight fell by 9.9% and her blood pressure decreased from an average of 152 systolic and 112 diastolic to 142 systolic and 108 diastolic.

Two other patients (Cases 13 and 14) were unable to tolerate ammonium chloride due to the occurrence of nausea, vomiting, and acidosis within 48 hours of its first administration.

Four patients, in addition to the 24 referred to above, with normal blood pressures in the last trimester of pregnancy, received 16 gm. of ammonium chloride daily for 1 week. Weight losses of 4.6, 5.0, 5.7, and 5.8% occurred. There were no consistent blood pressure changes.

IV. It is remotely possible that the 10 women with hypoproteinemia would have developed the changes recorded even if sodium had not been administered. Accordingly, 6 other women, whose condition was comparable to the 10 of Group II, with calculated plasma oncotic pressures varying from 206 to 220 mm. of water, were placed on a daily diet consisting of 260 gm. of protein, 100 gm. of carbohydrate, and 50 gm. of fat immediately upon admission to the hospital. No sodium other than that contained in the food or taken as seasoning on the food was administered. It is apparent from Table 3 that no significant change occurred in blood pressure or albuminuria. Rather than gains in weight, weight losses of from 2.9 to 4.1% occurred in 1 week's time. In no case did symptoms appear to become worse. A typical case has been charted (Chart X).

Discussion. It is generally conceded that only women who gain weight excessively during pregnancy develop the signs and symptoms of true "toxemia."[5] Previously[6b] evidence was presented which suggested that this excessive gain in weight was the result of water retention with either occult or gross edema. Further it was indicated that this water retention resulted not from hormonal influences or renal disease, but was the simple effect of lowered oncotic pressure of the plasma proteins. It was also shown that concomitant with a loss of retained water following the administration of a high protein diet the signs and symptoms of "toxemia" abated. In the present study, it has been shown that water retention may be induced in pregnant women, as in non-pregnant subjects, by the administration of sodium salts, and that the degree of retention varies inversely with the oncotic pressure of the plasma proteins. The difference in behavior of women with low oncotic pressures and those with normal pressures is quantitative rather than qualitative insofar as water retention is concerned. It has further been shown that pregnant women with low plasma proteins, who exhibited rapid and marked water retention following the administration of sodium salts, concomitantly developed rises in arterial blood pressure, and in 5 instances increased albuminuria. In 3 of the 10 cases studied symptoms and signs of "pre-eclampsia" appeared. With our present state of knowledge concerning the nature of arterial hypertension it would be foolhardy to speculate on the mechanism involved in producing the hypertension in the pregnant women studied. The fact remains that rapid gains in weight were accompanied by rises in arterial blood pressure.

In previous papers,[6a,b] it was indicated that lowered plasma proteins could result from a variety of factors, such as poor protein intake, protein loss, and malabsorption, and possibly failure of protein manufacture—all in the presence of the fetal demand for protein building materials. The importance of preventing the operation of the first factor by supplying an adequate amount of dietary protein to all pregnant women has been pointed out.

Summary and Conclusions. 1. Sodium given to 10 pregnant women with hypertension and hypoproteinemia resulted in significant weight gains, the occurrence of visible edema, and rises in the arterial blood pressure in each instance. In 5 women albuminuria increased and in 3 symptoms of pre-eclampsia appeared.

2. An identical amount of sodium given to 8 pregnant women with hypertension but no hypoproteinemia resulted in small increments of weight but was without other effect.

3. Ammonium chloride given to 3, and a high protein diet to 6, pregnant women with hypertension and hypoproteinemia resulted in significant weight losses and declines in arterial blood pressure.

4. The evidence presented suggests that the manifestations of "toxemia" of pregnancy in the patients studied resulted from water retention conditional upon hypoproteinemia.

5. The administration of sodium is dangerous in pregnant women with hypoproteinemia. The bicarbonate is fully as dangerous as the chloride. Its indiscriminate use in pregnancy is contraindicated.

The writer is indebted to Dr. F. H. L. Taylor and Miss Margaret Adams for carrying out the chemical determinations reported in this paper.

This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

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A HUMAN GALL STONE COMPOSED OF CALCIUM PALMITATE.

By A. T. Cameron, D.Sc.,
Professor of Biochemistry, University of Manitoba,
and
F. D. White, Ph.D.,
Assistant Professor of Biochemistry, University of Manitoba,
Winnipeg, Canada.

The gall stone which will be described was essentially a calcium soap, a type extremely rare. We could only find 3 other such cases in the literature; that most similar dates back to 1847. A complete

examination of the many papers dealing with biliary calculi might reveal a few more like cases; unfortunately the titles of such papers seldom give a clue to the composition of rare stones, even when hinting at unusual nature.

Case History. J. M., male, aged 64, was admitted to the Winnipeg General Hospital on February 6 last, complaining of general malaise, and of having been ill for the previous 18 months. He was senile and non-coöperative, no accurate information of his previous illness could be obtained, and no definite symptoms were apparent. He was placed on a light diet, without other treatment, and kept under observation. His temperature and pulse were normal until February 19, when the former rose to 102° F. (subsiding next day), but his pulse increased and remained above normal. There were still no other definite symptoms. He died on the 21st, of lobar pneumonia.

At *autopsy* (Dr. Sara Meltzer, Assistant Pathologist) the only pathologic findings, other than presence of empyema and a pleural exudate, were associated with the liver and the gall bladder. The liver weighed 1800 gm., and was smooth and dark red in color. The cut surface showed yellowish areas and was softer than normal. Microscopically, there was some slight fatty degeneration. "The gall bladder is large and pale, and contains thin yellow bile. There is also a single calculus of very unusual appearance. It is elongated, 3.5 cm. in length, and 1 cm. in diameter. The surface is yellow. On section it shows a small dark mixed nucleus, but the greater part of the calculus is yellow, firm, and homogeneous." The stone was lying free in the gall bladder, and there was no evidence of any occlusion of the duct. Microscopic examination of the gall bladder showed no inflammatory change.

Dr. Meltzer was kind enough to give the stone to one of us for chemical examination.

Examination of the Gall Stone. The stone, as received in two pieces, weighed 2.25 gm. The material was somewhat friable, with a soapy feel; there was a suggestion of concentric structure. The stone was of canary-yellow color throughout, except for a small brownish-black portion near the center.

The yellow material appeared to be practically insoluble in water, alcohol, acetone, chloroform, and benzene, and in hot dilute sodium hydroxide. After treatment with chloroform, the solvent gave a negative Salkowski and a doubtful Liebermann reaction for cholesterol. The material (0.1 gm.) was thoroughly extracted with ether and the ether evaporated; an unweighable trace of solid remained, which was extracted with chloroform. The extract gave with the Liebermann test a purple color, changing to bluish. This result seems to exclude cholesterol, and suggests that a trace of a cholic acid or similar compound was present.

None of the lipoid solvents extracted the yellow color.

A trace of the original material was heated in a nickel spoon; it burned with a smoky flame, and left a white ash. The flame test showed the presence of calcium, but indicated that not more than the faintest trace of sodium was present. The 2.4 dinitrophenol "spot" test for potassium[8] was negative.

The yellow material dissolved readily in cold glacial acetic acid, and addition of water to the solution threw down a heavy precipitate which retained the yellow color. When the precipitate was boiled with dilute acetic acid, and then cooled, pure white crystals separated. The yellow supernatant acid fluid changed slowly in color on standing to a definite green, indicating that the original color was due to calcium bilirubin, and

that the freed bilirubin had slowly changed in solution to biliverdin. The white crystals were easily soluble in chloroform and other lipoid solvents.

The behavior of the yellow material strongly suggested that it consisted of a calcium compound of one or more fatty acids. Accordingly the crystals thrown down from acetic acid were recrystallized from aqueous alcohol, and their melting point determined to be 62 to 63° C. Palmitic acid melts at 62.6° and stearic acid at 69.3° C. On account of Thudichum's results, referred to later, indicating that a melting point of the order found might be due to stearic acid contaminated with a trace of oleic acid, removable from it with difficulty, the recrystallized material was further twice recrystallized from aqueous alcohol. The product still showed the same melting point. It was then fractionated from aqueous alcohol, but the first fraction (which should contain any stearic acid) showed the identical melting point. Finally, since Scheringa[10] has shown that potassium palmitate is ten times more soluble in 49% alcohol than is potassium stearate, this therefore affording a good method of separating these acids, the purified acid was dissolved in absolute alcohol and potassium ethylate added, the precipitated potassium soap was filtered and dried, and then dissolved in 49% alcohol, in which it was found to be very soluble. The solution was acidified and water added, reprecipitating the original acid, which was once more recrystallized from aqueous alcohol; the product gave the melting point 62 to 63° C. (corr.). A mixture of this product with purified palmitic acid of correct melting point gave exactly the same figure. Hence we conclude that the acid obtained from the stone was pure palmitic acid, and that stearic acid was absent. The iodine number was zero, supporting the conclusion that oleic acid was also absent.

These conclusions were confirmed by estimations of the acid value by titration with N/50 alcoholic sodium hydroxide. These were carried out with pure palmitic and stearic acids, and with the original recrystallized acid, before preparation of the potassium salt. Fifty or 60 mg. were used for each titration, and the results have been calculated to 100 mg. for comparison. Duplicate determinations were made in each case.

Pure stearic acid required	(i) 17.63 cc.	Mean, 17.66 cc.
	(ii) 17.68 cc.	Theory, 17.61 cc.
Pure palmitic acid required	(i) 19.42 cc.	Mean, 19.49 cc.
	(ii) 19.56 cc.	Theory, 19.53 cc.
The unknown acid required	(i) 19.37 cc.	
	(ii) 19.61 cc.	Mean, 19.49 cc.

Part of the stone (0.5040 gm.), containing an approximately proper proportion of the dark center, was dissolved in glacial acetic acid, and centrifuged to remove some brownish-black insoluble material, which, after drying, amounted to 0.0245 gm. (4.86%). The solution, with washings from the insoluble portion, was diluted with water until no further precipitate was thrown down. The yellow precipitate was filtered off, washed, and dried to constant weight at 37° C. It weighed 0.4045 gm. (80.3%). By virtue of the exact examination already described, this precipitate was considered to consist of palmitic acid, colored by a trace of bilirubin. A portion (49.5 mg.) was dissolved in 10 cc. of chloroform, and compared in a colorimeter with 0.16 mg. of pure bilirubin also dissolved in 10 cc. of chloroform. The colors matched perfectly, and the comparison indicated the presence of 0.18 mg. of bilirubin in the quantity assayed, representing 0.36% of the original material; the true figure for palmitic acid was therefore 79.9%.

The filtrate from the palmitic acid was evaporated to dryness, the residue dissolved in dilute hydrochloric acid, neutralized with sodium hydroxide, and made up to known volume. Calcium was estimated by Clark and

Collip's method,[2] which gave the figure 43.7 mg. for the total solution, corresponding to 8.7% of the original material.

Some (0.1425 gm.) of the original material was ignited to constant weight. The ash weighed 0.0220 gm. (15.4%). It was dissolved in dilute hydrochloric acid and made up to known volume. Phosphate was estimated in the solution by the method of Benedict and Theis,[1] and amounted to 0.0055 gm. as PO_4, calculated to the total quantity taken (3.9%). The solution also contained magnesium, but in unestimable amount; the ammonium thiocyanate test showed presence of a trace of iron.

The brownish-black material insoluble in glacial acetic acid was examined separately. When a trace of it was warmed with 10% sodium hydroxide, a small proportion dissolved to a green solution. This was thought to be adherent biliverdin. The bulk of the material did not dissolve. This residue gave a negative Gmelin's test for bile pigment, although it slowly dissolved in strong nitric acid, apparently through oxidation. It was considered to be the ill-defined ultimate oxidation product of bilirubin usually termed "bilihumin."

Some of the brownish-black material (8.3 mg.) was strongly ignited to constant weight; 1.5 mg. of gray ash was left, which contained calcium, phosphate, and a trace of magnesium (detected by the Titan-yellow test[6]). This mineral matter is, at least in part, already included in the estimations of phosphate, and, correcting for it, the bilihumin content of the original material is approximately 4.0%.

Some of the original material (82.3 mg.), heated to 105° C. to constant weight, lost 2.2 mg. of water, 2.7%.

Conclusions from the Analyses. Since 79.9% of palmitic acid was found, this required 6.2% of calcium for complete combination. The phosphate (PO_4), 3.9%, required 2.5% of calcium for combination as $Ca_3(PO_4)_2$. The total calcium required, therefore, agreed with the 8.7% found (but the brownish-black material also contained a trace, which was not estimated). It can be concluded with reasonable certainty that calcium palmitate and tribasic calcium phosphate account for practically all the palmitic acid, phosphate, and calcium found.

The ash, 15.4%, can be similarly accounted for. The calcium oxide corresponding to 79.9% of palmitic acid equals 8.7%, which, added to 6.4% calcium phosphate, gives a total of 15.1%. Other mineral constituents could only be present in traces.

Hence the composition of the calculus can be stated fairly accurately as:

Calcium palmitate	85.8%
Calcium phosphate	6.4%
Calcium bilirubin	0.4%
"Bilihumin"	4.0%
Iron, magnesium	Traces
A cholic acid (?)	Trace
Water	2.7%
Unaccounted for	0.7%
	100.0%

Roentgen Ray Examination. A Roentgen ray photograph* of somewhat less than half the stone, taken through 8 inches of paraffin

* We are indebted to Dr. H. M. Edmison, Assistant Radiologist to the Winnipeg General Hospital, for this photograph.

wax, showed a distinct and fairly even opacity, indicating an even distribution of calcium salts throughout the stone, and probably indicating that such a stone could be detected during life.

Discussion. Frerichs[4] in 1847 found that a human gall stone from the museum at Gottingen contained 68% calcium palmitate and 28% cholesterol. Fatty acid crystals prepared from the stone melted at 58° C., which suggest that they were not pure palmitic acid. Thudichum (1863)[11] analyzed a gall stone from John Hunter's collection. It yielded fatty acid crystals which melted at 60° C., but repeated recrystallization from hot alcohol gave a fraction melting at 71° C. His analysis indicates that the stone contained 84% of calcium stearate (including a trace of oleate); cholesterol was absent. Fouquet (1896)[3] analyzed a gall stone consisting largely of calcium stearate and phosphate, with but a trace of cholesterol. Identification of fatty acid crystals prepared from the stone seems to have been based on a melting point of 70° C. and the crystal form. He was unaware of the earlier reports.

Thudichum refers to presence of traces of calcium soaps in ordinary gall stones. Salkowski[9] found traces of fatty acids (chiefly palmitic acid) in mixed cholesterol and pigment stones, with less calcium than corresponded to them. He made no reference to the above reports. Classifications of biliary calculi, subsequent to that of Thudichum, do not list calcium soap stones.

The present report seems to be the first of this type associated with a case history, and, unfortunately, that history gives no clue to the mechanism of formation of the stone. Little can serviceably be said on this point. Passage of soluble soaps from intestine to gall bladder should lead to a mixed calcium soap, were this formed, instead of the calcium palmitate here reported; such passage is in any event extremely improbable.

Bile usually contains traces of soluble soaps, and of calcium.[5,7] Calcium soap stones are probably formed from biles containing such constituents in unusual proportions, and illustrate a rare type of aberrant metabolism. To theorize further seems unprofitable at present.

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END-RESULTS FOLLOWING CHOLECYSTECTOMY.

By Ralph B. Bettman, M.D.,
ATTENDING SURGEON, MICHAEL REESE HOSPITAL; ASSOCIATE PROFESSOR OF CLINICAL SURGERY, RUSH MEDICAL,
AND
Gemma Lichtenstein, M.D.,
CLINICAL ASSISTANT IN MEDICINE, MICHAEL REESE HOSPITAL,
CHICAGO, ILL.

(From the Surgical Department of Michael Reese Hospital—Gall-bladder Group.)

To the many analyses of the results following upon cholecystectomies, we are adding ours in the hope that out of these studies there may arise better criteria for determining what types of patients will secure sufficient relief from the operat on to justify the measure. At present, despite careful study of each patient who comes under our care, and despite judicious selection of the patients with cholecystitis or cholelithiasis or both, we find a disappointingly large group who have little or no relief from the symptoms for which the cholecystectomy was performed.

From January 1, 1930, to December 31, 1934, there were 239 cholecystectomies performed on the charity division of this hospital, omitting all private patients. Of this number, 33 had some type of common duct operation at the same time. Furthermore, during this period there were many cholecystotomies, explorations of the gall bladder and biliary tract operations which are not included, because we have limited this study to the effect of cholecystectomy for benign lesions.

Ten of the patients died, making a mortality of 4.2% for the whole series. Of the 33 patients with common duct drainage, 4 died: a mortality for this subgroup of 12.1%. One of these deaths was probably due to coronary occlusion. Of the 206 patients with simple cholecystectomy, 6 died: a mortality of 2.9% for this subgroup. These deaths included 3 patients: 1 of 55 years who had a coronary occlusion with sudden death a few hours after operation; 1 of 58 years who came in with hypertension and decompensation and jaundice and died of pneumonia; a third patient of 65 with diabetes and chronic myocarditis who developed a thrombophlebitis of the right leg 10 days postoperatively and finally died of pneumonia. This leaves 3 cases (1.5%) who may be considered as straight operative deaths. In a larger group of 1624 patients with gall-bladder operations of all types, and including private and charity patients, there were 68 deaths, or again 4.2% mortality.

Of the 239 patients, 208 were females and 31 were males. The ages ranged from 16 to 70 years with 76 (32%) between the ages of 31 and 40, and 74 (31%) between the ages of 41 and 50; in other words, about two-thirds of the patients were in the fourth and fifth decades (Table 1).

TABLE 1.—AGE INCIDENCE.

	Male.	Female.
11–20	..	6
21–30	45	39
31–40	8	68
41–50	10	64
51–60	7	24
61–70	1	6
Unknown	..	1
Total	31	208

Symptoms. One hundred and sixty-eight patients had demonstrable gall stones. In this series the predominant symptom was pain in the right upper quadrant and epigastrium; this occurred in 163 cases (97%). In the great majority there was a history of radiation of the pain. Nausea was the second most common symptoms occurring in 132 patients (79%). Vomiting occurred in 62% of the cases; belching in 53%. Food idiosyncrasy was a definite complaint in somewhat less than half of the cases. Bloating occurred in a third, and jaundice was present in 46 (27%). Heartburn was complained of in a fifth of the cases. Fevers and chills and clay-colored stools were present in approximately 1 out of 10 cases (Table 2).

TABLE 2.—INCIDENCE OF SYMPTOMS.

Symptom.	Cases with stones. Per cent.	Cases without stones. Per cent.
R.U.Q. Epigastric } pain	163 (97.0)	66 (93.0)
Radiation of pain	121 (72.0)	42 (59.2)
Bloating	57 (33.9)	29 (40.8)
Belching	89 (53.0)	36 (50.7)
Heart burn	34 (20.2)	15 (21.1)
Nausea	132 (78.6)	56 (18.9)
Vomiting	104 (61.9)	39 (54.9)
Food idiosyncrasy	70 (41.7)	30 (42.3)
Fever and chills	22 (13.1)	7 (9.9)
Constipation	72 (42.9)	31 (43.7)
Melena	11 (65.0)	4 (5.6)
Clay stools	23 (13.7)	9 (12.7)
Jaundice	46 (27.4)	19 (26.8)
Headache	7 (4.2)	8 (11.2)

In 71 patients no stones were found at operation. In this series pain again was the predominating symptom, occurring in 93%, and here again the pain radiated in over half of the cases. Nausea was present in almost the exact proportion as in the group with stones (80%). Vomiting was present in 55%; belching in 51%. Food idiosyncrasies were also found in a little less than half. Bloating was slightly more common than in the group with stones, being present in about 40%. Jaundice was present in 14 cases (27% of this series). Interestingly enough, jaundice is seen to be present to almost the same extent in those patients who had no stones in their gall bladders at the time of operation as in those who had

calculi. We cannot help but wonder whether, in those patients who had been jaundiced but in whom no stones were found, there had at some previous time been calculi which had made their way down the ducts and into the intestines; also, if these gall bladders were to be left *in situ*, would calculi again form? Heart burn, chills and fever, and clay-colored stools were as frequent in this group as in the group in whom stones were found at operation. None of these patients was jaundiced at time of operation and none has had jaundice since, so that we feel that in these cases we have not overlooked common duct stone (Table 2).

Results. In evaluating our results, we have omitted 55 patients whom we were not able to trace. From the remaining 184, we have subtracted the 10 deaths, leaving 174 patients followed for a period ranging from 1 to 6 years. Of these 174 who had cholecystectomies, 119 had stones and 55 had none.

In order to obtain some basis for the analysis, not only for ourselves but for the literature as well, we have divided the results into three distinct groups: 1, symptomatic cure; 2, symptomatic improvement; 3, no relief. By "symptomatic cure" we mean a complete subsidence of all the pre-operative symptoms which prompted cholecystectomy. By "symptomatic improvement" we mean relief of the major symptoms, a definite improvement in the well-being of the patient and a very definite affirmative response to the question "Do you think that the operation was worth while?" By "no relief" we mean that there was no outstanding subsidence of symptoms, and although occasionally the patients might affirm that the operation had been of help, yet they still suffered from the majority of their pre-operative complaints.

Study of Cases With Gall Stones. There were 119 cases of cholelithiasis, not counting the 7 who died in the hospital. Symptomatic cures were obtained in 66 (55%); symptomatic improvement in 32 (27%); and no relief in 21 (18%). In other words, only 82% of the patients were definitely improved by operation (Table 3).

TABLE 3.—RESULTS.

	With stones (126). Per cent.	Without stones (58). Per cent.
Sympt. cure	66 (55)	25 (45)
Sympt. improv.	32 (27)	12 (22)
No relief	21 (18)	18 (33)
Deaths	7	3

In comparing the results of the operation with the pathologic findings we noticed, strangely enough, that the percentage of good results increased with the severity of the lesions encountered in the gall bladder. From a pathologic point of view, the gall bladders in these patients were divided into five groups: 1, those with no demonstrable gross or microscopic lesion of the gall bladder wall; 2, those with fibrosis; 3, those with chronic cholecystitis; 4, those

with marked chronic cholecystitis; and 5, those with acute cholecystitis.* From a pathologic standpoint we might assume a progression of the disease from the first to the fourth of these categories.

Symptomatic cures were obtained in Group 2 (fibrosis) in 32% and symptomatic improvement in 41%, leaving no relief in 27% of the patients. In Group 3 (chronic cholecystitis) symptomatic cure was obtained in 58%, symptomatic improvement in 28%, and no relief in 14%. In Group 4 (marked chronic cholecystitis) presumably the group in which the disease had lasted the longest or had made the severest inroads, symptomatic cure was obtained in 67%, symptomatic improvement in 13%, and no relief in 20%. In other words, the patients falling into Group 4 had a symptomatic cure twice as often as those in Group 2 (Table 4).

TABLE 4.—LESIONS FOUND IN THE GALL BLADDER.

	Cure. Per cent.	Improv. Per cent.	No relief. Per cent.	Death
With Stone.				
No chge.	4			
Fibrosis	7 (32)	9 (41)	6 (27)	1
Chr. cholec.	44 (58)	21 (28)	11 (14)	5
Marked chr. cholec.	10 (67)	2 (13)	3 (20)	1
Ac. cholec.	1		1	
Without Stone.				
No chge.	1 (25)	2 (50)	1 (25)	
Fibrosis	12 (48)	5 (20)	8 (32)	
Chr. cholec.	8 (38)	5 (24)	8 (38)	1
Marked chr. cholec.	4 (80)		1 (20)	2

In an endeavor to see if there were any correlation between the length of duration of the symptoms and the degree of the lesion, we tabulated our cases with this in mind. Interestingly enough, the various histopathologic divisions had about the same relative number of cases, irrespective of whether the symptoms were of less than 1 year's duration, from 1 to 2 years, from 2 to 3, from 3 to 5, or from 5 to 10 years. In the group complaining of symptoms for more than 10 years, we find a very slightly elevated number in the marked chronic cholecystitis group.

The duration of the symptoms varied greatly, from a few months to many, many years. It would seem likely that the shorter the duration of the symptoms the greater the percentage of benefits; this was only partially borne out by our findings, namely, that in patients with symptoms for less than 2 years, 87% had symptomatic cure or improvement and only 13% had no relief; with symptoms of from 2 to 5 years' duration, 80% were cured or improved and 20% had no relief; with symptoms of from 5 to 10 years, 96% were cured or improved, and 4% had no relief; but when symptoms had been present for over 10 years only 58% were cured or improved

* There were 2 patients in this group with microscopic findings of an acute lesion, although clinically both patients were considered non-acute.

and 42% had no relief. It seemed peculiar to us that the group having symptoms for a period of 5 to 10 years should have shown better results than those having symptoms for a shorter period. However, this correlates with our observation that symptomatic cure was commonest where change was severest, that is, in those patients whose gall bladders showed marked chronic cholecystitis.

When we check our results against the age of the patients, we find the poorest results in the age groups of 11 to 20 and 51 to 70 years; the best results between the ages of 21 and 40 years, with nearly as good results between the ages of 41 and 50 (Table 5).

TABLE 5.—RESULTS BY AGE INCIDENCE.

With Stones.

	Cure. Per cent.	Improv. Per cent.	No relief. Per cent.	Death.
Unknown		1		
11–20	1 (25)	2 (50)	1 (25)	
21–30	11 (58)	6 (32)	2 (10)	1
31–40	17 (53)	12 (38)	3 (9)	1
41–50	28 (62)	9 (20)	8 (18)	1
51–60	9 (53)	2 (12)	6 (35)	2
61–70			1	2
	66	32	21	

Thirteen patients had had a cholecystostomy at some previous date; of these, 4 had relief for less than 1 year, 4 from 1 to 5 years, 2 were relieved for a period of 6 or 7 years, and 3 for over 10 years.

Of the patients, 33 had a drain inserted into the common duct in addition to the cholecystectomy. The common duct was drained either because stones were palpable in the duct, or because the duct was greatly distended, or because of jaundice either before or at the time of operation, leading us to suspect a stone. Three of these were patients in whom no stone could be found either in the gall bladder or in the common duct. One of these died as a result of periportal infection. The other 2 had symptomatic cures. Of the 30 patients with cholelithiasis who had common duct drainage, 3 died; 15 had symptomatic cures, 6 had symptomatic improvement; or, in other words, 78% had cure or improvement and 22% had no relief. If one combines the non-calculous and the calculous group with common duct drainage, we find that there were 4 deaths, that is 12% of the cases of common duct drainage. We do not have a large enough series of cases with common duct drainage to draw conclusions of any real worth; but we would like to point out that the mortality rate is 4 times as high as in simple cholecystectomy.

Non-calculous Cases. For many years we have felt that our results after cholecystectomy in patients without gall stones have been poor. For this reason we have refrained from operating unless there has been definite evidence of stones either by Roentgen ray or from a history of repeated gall-bladder colic. Therefore, nearly

all the cholecystectomies reported in this group had so-called typical symptoms (Table 2).

There were 58 patients (including 3 who died postoperatively) who had no gall stones either in the gall bladder or ducts whom we have followed for at least a year since they had a cholecystectomy. Of those living, 25 had symptomatic cure and 12 had symptomatic improved (67% cured or improved), while 33% had no relief. It is interesting to compare these figures with those of the group with calculi, where 82% were cured and improved and only 18% had no relief. We think that small as this group may be and in view of the careful selection of cases for operation, that this is a very significant difference (Table 3).

Studying this group of non-calculous cholecystectomies, from a histopathologic point of view, we find marked gall-bladder changes which may or may not account for the symptoms. Fibrosis was present in almost half of the cases, chronic cholecystitis in about 40% and marked chronic cholecystitis in about 9%. These findings support our previous contention that many of these gall bladders may have contained stones at some earlier date. As in the group with stones, the best results were obtained in those cases showing marked chronic cholecystitis.

Regarding any correlation between the length of duration of symptoms and the degree of damage present, we can only say that we were unable to discover any.

The duration of symptoms seemed to effect the results somewhat, namely, that in this group the better results were obtained in those having had symptoms for less than 5 years, 75% cured or improved, and 50% cured and improved in those having had symptoms for more than 5 years.

When we compare our results to age incidence, we find that regardless of the decade about a third of the patients had no relief.

Four of the patients in this group had had a cholecystostomy at some previous time; 2 had had relief for less than 1 year, 1 had relief for 4 or 5 years, and 1 for 6 or 7 years.

Summary and Conclusions. 1. Of 239 patients with cholecystectomies performed from 1930 to 1935 on the charity service, 31 were men and 208 women; about 63% were between 31 and 50 years.

2. Epigastric and right upper quadrant pain was the most common symptom in both calculous and non-calculous types of cases.

3. Seventeen patients had previous cholecystostomies, of whom 8 had relief for less than 3 years.

4. There were 10 deaths, or 4.2% of the cases in the entire series, including all types of complications. Of these 33 cases with common duct drainage in addition to the cholecystectomy, the mortality rate was 12.1%, leaving a mortality of 2.9% for all cases in which cholecystectomy alone was done. This figure includes all

cases irrespective of age, acuteness of gall-bladder lesion, cardiac failure or other unforeseen postoperative events.

5. Of 119 patients with calculous gall bladders who had been followed more than 1 year, 55% had symptomatic cure; 27% had symptomatic improvement and 18% had no relief, or 82% cured or improved by operation.

6. Of the patients with non-calculous gall bladders, 58 were studied: 45% had symptomatic cure, 22% symptomatic improvement, and 33% had no relief.

7. It seems that the best results are obtained in those cases where stones are present. Furthermore, that the more definite the symptoms the more apt there is to be complete recovery from operation.

8. Searching the literature we find a great variance in reports and a surprising inconsistency in the percentage of cures. One thing, however, appears certain, and that is that all is not as it should be in gall-bladder surgery.

9. We believe that continued and careful studies of large series of patients who have been operated upon for benign disease of the biliary tract will aid in establishing better standards by which to select those patients in whom results will justify the risks of operation.

BUNDLE BRANCH BLOCK WITH SHORT P–R INTERVAL IN INDIVIDUALS WITHOUT ORGANIC HEART DISEASE.

CASE REPORT WITH REVIEW OF LITERATURE.

BY LOUIS FAUGERES BISHOP, JR., M.D.,
ASSOCIATE VISITING PHYSICIAN, BELLEVUE HOSPITAL,
NEW YORK.

THE peculiar syndrome called bundle branch block with short *P–R* interval in individuals without organic heart disease has aroused great recent interest. A late experience with this condition has led to a review of the literature and a report of a case. Although it is true that the number of reported cases is small—to date only 45—it seems apparent from the rate with which reports are now appearing that this condition will soon be recognized as not infrequent. Aside from the increase in general interest this is one of the gratifying disorders encountered in medicine, gratifying because the diagnosis can be made with absolute certainty with the aid of the electrocardiogram, and once made, one can give the patient and his family complete assurance that his disorder will not shorten his life nor restrict his activity in any way.

Review of Literature. The first reported case, a man, aged 23, with attacks of paroxysmal tachycardia for 11 years, was described and carefully reported by Wilson[13] in 1915. Wedd[12] reported the

next case in 1921, and Hamburger[4] in 1929, but not until a year later when Wolff, Parkinson, and White[15] collected and reported 11 cases, with careful follow-ups to 4 years, did the phenomenon become a clinical entity. The work of these three men soon stimulated interest in cardiologic circles all over the world, with the result that there has been a steady increase in the number of recorded cases since 1930. To wit: Pezzi[7] reported 3 cases in 1931, Holzmann and Scherf[5] 2 in 1932. Wolferth and Wood[14] reported 9, and Sigler[9] 1 in 1933.

In the past year there have been several single and multiple case reports from various parts of the world. Roberts and Abramson[8] reported 1 case. Sprague[10] recently added a case associated with paroxysms of auricular fibrillation without any other evidence of organic heart disease. Faxen[3] reports from Sweden an example in a boy of 11. From Peiping, Tung[11] reports 2 cases in detail, and mentions 3 others.

The most enlightening of last year's communications came from the Argentine, where Cossio, Berconsky and Kreutzer[2] reviewed 27 cases from the literature, added 7 of their own, and analyzed the group statistically from the standpoint of age, sex, type of tachycardia, presence or absence of coincidental organic heart disease and remission to a normal electrocardiographic configuration.

Case Report. Two years ago an opportunity was offered to observe an example of this condition. The patient was the only son of a Spanish family living in Mexico, referred by their doctor for an opinion and advice regarding a strange myocardial disorder. Attention had been directed to his heart because of a short attack of paroxysmal tachycardia which had occurred while climbing a mountain. Medical advice was sought immediately, but on physical examination no abnormal findings were disclosed, and the patient and family were reassured. Three months later there was a second attack while descending a flight of stairs. This was associated with slight palpitation, dryness of the mouth, headache and a pulse rate of 220. Again the duration of the attack was short. An electrocardiogram taken after the attack showed a widened *QRS*, and a notching of the *R* waves, suggestive of an incomplete bundle branch block, and in addition an abnormally short *P–R* interval. Search for an etiologic factor disclosed a faintly positive blood Wassermann reaction, and though the Wassermann of both parents was negative, the patient was given a series of 12 intramuscular injections of colloidal bismuth. The boy was taken out of school and kept under strict medical supervision for 7 months. During this time four electrocardiograms were taken, no two of which were exactly alike, but all four consistently showed a short *P–R* interval, a widened *QRS*, and slurring of the *R* wave. There were no more attacks and at no time was there any evidence of cardiac insufficiency.

His history revealed nothing suggestive of a familial disorder; there are 2 younger sisters who are perfectly well. His health was first interrupted at the age of 4 by a disorder of the lower bowel which was said to be colitis; this cleared up in 3 months and has not recurred. At 5 he had measles, followed by whooping cough; 6 months later he had a series of attacks of fever and headache, with normal health between. Following some sort of vaccine therapy the attacks disappeared and have never recurred. For the remainder of his childhood and early puberty he enjoyed good health and a normal

school life. He has never had scarlet fever, diphtheria, tonsillitis, or any rheumatic manifestations.

His family brought him to New York in December, 1936, after spending a harrowing 7 months closely guarding his health and activity and being constantly fearful of the outcome of his disorder.

On physical examination he appeared to be a tall, thin, somewhat lethargic boy of 14 who looked perfectly well. The blood pressure was a little below the usual level—100/60, but the remainder of the physical examination was entirely negative.

Laboratory findings disclosed a 3+ albumin in his urine, with rare hyaline and granular casts on centrifuged specimen. This finding was at first disturbing, but repeated specimens obtained before getting up in the morning were entirely clear, while those after standing showed albuminuria. It was concluded that his albuminuria and microscopic findings were on a functional orthostatic basis. Complete blood count, erythrocyte sedimentation rate, blood non-protein nitrogen and blood sugar were all within normal limits. Basal metabolic rate was −21, which may have accounted for his apparent lethargy. Wassermann and Kahn tests, done by different laboratories, were negative.

Electrocardiograms showed the same abnormal graph, previously observed in Mexico, namely a short *P–R* interval, a widened *QRS* and slurring of the upstroke of the *R* wave (Fig. 1). As the clinical and electrocardiographic findings seemed identical with the cases described by Wolff, Parkinson and White,[15] and as the abnormal graph could be abolished in their cases by the use of atropine or exercise, an attempt was made to determine whether this patient might also respond electrocardiographically to these stimuli.

An electrocardiogram of Lead I (Fig. 2 *B*) was taken immediately after exercise (jumping up and down on one foot for 1 minute) and when compared with the control (Fig. 2 *A*) shows slight but definite changes. The *P–R* interval is lengthened from 0.8 to 0.12 second; the *QRS* shortened from 0.1 second to 0.04. The thick slurring of the upstroke of the *R* wave is eliminated and the *QRS* takes on a normal configuration with slight increase in voltage. The change was so transient that it was lost in the change of Leads, so that in Lead II (Fig. 2 *C*) taken only a few seconds after Lead I (Fig. 2 *B*), there is a return to the original abnormality. Following the subcutaneous injection of 1/50 grain of atropine there was no change in the electrocardiogram; likewise no change was effected with 2 days of belladonna fluid extract 15 minims t.i.d. by mouth. Vagal pressure was attempted immediately after exercise and during the taking of an electrocardiographic tracing to determine whether the changes to normal following exercise could be prematurely reversed by this form of vagal stimulation. Exercise produced such a transient effect that it was impossible to determine in the vagus pressure experiments whether the change back to the old configuration was ever hastened by vagal stimulation. The diagnosis established, the family could be assured that the boy was not suffering from any form of organic heart disease. Although he has not returned to New York, current communications with the family indicate that he has been living a normal life for his age in a preparatory school in Texas, and engaging in athletic activities, and has had no recurrences of his attacks of tachycardia.

Discussion. Comparison of this case with others, showed that the clinical and electrocardiographic features of this syndrome are clear cut—certainly well within the general variability of clinical syndromes. Usually occurring in young individuals of the athletic type, it is seen much more frequently in males than in females.

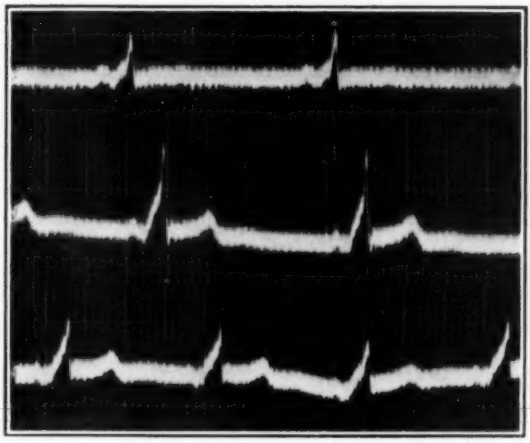

FIG. 1.—Electrocardiogram (5694), December 24, 1935. Intraventricular conduction defect with short *P–R* interval. *P–R*, 0.08 sec.; *QRS*, 0.1 sec.

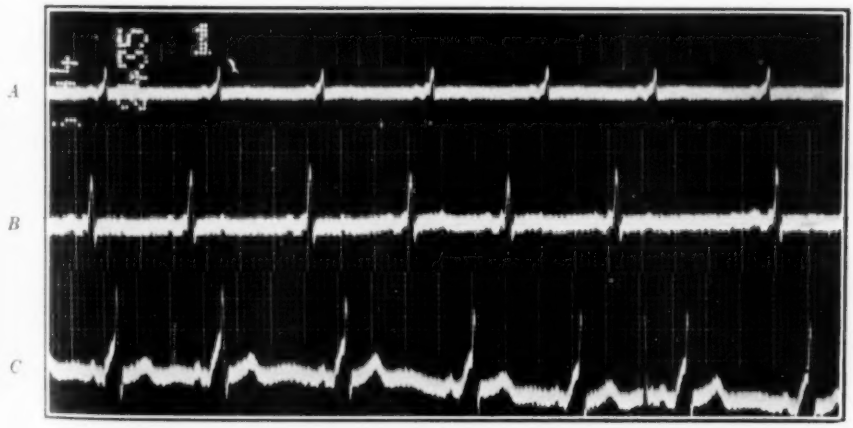

FIG. 2.—Electrocardiogram (5694), December 24, 1935. *A*, Lead I: control; *B*, Lead I: after exercise; *C*, Lead II: taken immediately after *B*.

It has been found in individuals in all age groups, from $4\frac{1}{2}$ to 62 years; but most frequently in the second, third and fourth decades, though the history usually dates back to puberty, or before, when the patient first began to experience periodic attacks of palpitation, sometimes induced by strenuous exercise, but almost as frequently occurring when the patient is at rest. There are, however, a few reported cases in which palpitation was never experienced. Whether or not these cases had tachycardia without palpitation, it is impossible to say. Wolferth and Wood[14] reported 4 cases discovered accidentally during a routine study of normal electrocardiograms, or through electrocardiographic findings, as part of a routine examination. And Tung mentions 2 with characteristic electrocardiographic findings, who gave no history of palpitation and who had never been known to have tachycardia. In 1 case in the series reported by Wolff, Parkinson and White,[15] the only cardiac symptoms were attacks of bradycardia associated with weakness and pallor. Although as a rule the presenting complaint is related to paroxysmal attacks of tachycardia, it becomes apparent that exceptions to this are not infrequent. This type of tachycardia, when present, is usually a simple paroxysmal auricular tachycardia. This was true in 39 of the 45 cases, while in the remaining 6 the tachycardia was on the basis of paroxysmal auricular fibrillation. (Wolff, Parkinson and White[15] report 1, Wolferth and Wood[14] 2, Cossio, Berkonsky and Kreutzer[2] 2, and Sprague[10] 1.)

Although there are a few cases in which organic heart disease is present, the type of organic involvement is so diverse, including hypertension with acute glomerular nephritis, inactive rheumatic heart disease, and hypertensive cardiovascular disease, it is hardly conceivable that organic heart disease when encountered is more than coincidental.

Remissions to normal electrocardiographic configurations may occur spontaneously and may be experimentally induced. Electrocardiograms taken during the attacks of tachycardia are usually normal. Sometimes they are found to be normal without tachycardia and for no apparent reason. Whether these remissions are ever permanent or not it is difficult to say, as there are not to date sufficiently long-time follow-ups on these cases definitely to answer the question. The data on the effect of atropine and exercise are conflicting. It is interesting to note that in some cases these methods of vagus inhibition do abolish the electrocardiographic abnormality, but the significance of these selected observations belongs in the realm of pure speculation.

Although one may suspect the existence of this condition in a healthy young individual—usually a male with a history of paroxysmal tachycardia without clinical or roentgenographic evidence of heart disease—the key to the diagnosis is to be found in the electrocardiographic findings that show a short P–R interval, associated

with a widening of the *QRS* and abnormalities in the initial ventricular complex characteristic of an incomplete or complete intraventricular conduction defect. The most usual type is a left bundle branch block, with the initial ventricular complexes as seen in left axis deviation and the *T* waves in Leads I and III in the opposite direction from the main complex. There are several reported examples of right bundle branch block and of intermediate stages of incomplete intraventricular block, as it was in this case. If it were not for the presence of the short *P–R* interval (*i. e.*, 0.1 second or below), these electrocardiograms could not be distinguished from organic bundle branch block or from the so-called functional bundle branch block, as described by Cohn and Lewis,[1] Sigler,[9] and others.

Views as to the etiology of this peculiar phenomenon are so diverse, experimental and clinical observations so contradictory, that it is impossible to reach any definite conclusions as yet. As there is no studied autopsy material available, it is conceivable that when obtained it may throw considerable light on the mechanism of the production of these electrocardiographic abnormalities. At present there is a sharp division between two schools of thought. One believes that it is a vagal effect induced by excess vagal tone which slows conduction through the bundle or one of its branches, relievable by suppression of the vagal influence by atropine or exercise. This was the view taken by Wolff, Parkinson and White,[15] and Wedd[12] found that vagal inhibition brought about a transition of the electrocardiogram to normal. The second view is that of Wolferth and Wood,[14] Holzmann and Scherf,[5] and Roberts and Abramson,[8] who were unable to confirm these observations. In their cases the abnormal graphs were not affected by vagal inhibition. They postulate that some aberrant conduction bundle is present between the right auricle and right ventricle, such as the bundle of Kent,[6] and that it is functionally able to transmit impulses. With this as a premise, they argue that the abnormal graph represents the passage of impulses through the pathway and that transition to the normal graph represents a return of the impulse to the normal pathway.

There are sufficient objections to both of these theories to make them untenable. With regard to the first theory, the following two facts have yet to be accounted for: (1) that there are many cases reported which show no effect from vagal inhibition; and (2) one case reported by Sigler[9] which reverted to a normal graph after vagal stimulation.

Against the theory of an abnormal conduction bundle is the fact that such abnormalities have not yet been demonstrated.

With respect to prognosis, it is true that the follow-up studies in known cases have been to date too short to be conclusive. Yet it is the unanimous opinion of those who have studied this condition that the disorder is primarily functional, and the patient's progress unaffected by the electrocardiographic abnormality. This view is

supported by the character of the history and clinical picture, and several reported cases in individuals past middle life who continue to show no evidence of cardiac insufficiency. It so happens that the oldest reported case is only 62, but he is in perfect health.

Treatment. It might be said that these patients are suffering from an electrocardiogram and not a disease. Therefore, medicinal treatment assumes no importance, but psychotherapy and reassurance are paramount. As has been pointed out before, the individual or the family may have been told that the patient is suffering from a bizarre form of incurable heart disease, and in consequence suffered an untold amount of mental anguish over this thought.

Completely to destroy this concept may require psychotherapy to prevent the development of a cardiac neurosis in the patient, which might otherwise become a permanent handicap. In this particular case it was not an easy task; the family had spent 7 months reconciling themselves to the fate before them and were almost reluctant to relinquish the state of martyrdom to which they had become accustomed.

The individual should be encouraged to live a normal life, and if, as is frequently the case, he is of school age or college age, he should be allowed to engage in athletics, unless the attacks of tachycardia become sufficiently frequent to interfere. In the reported cases, as well as here, attacks have not infrequently followed severe exercise. Continued exercise, however, does not seem to increase the frequency of the attacks, for they may well occur at rest. Apparently a small percentage of individuals seem to outgrow their electrocardiographic difficulties, and this permanent change seems to have no relationship to the extent of their activities.

Summary and Conclusions. 1. A peculiar electrocardiographic phenomenon is described, associated with a short $P–R$ interval, a widened QRS and slurring or notching of the QRS, characteristic of the so-called bundle branch block, except for the short $P–R$ interval.

2. One case is reported and 44 cases collected from the literature.

3. The condition occurs usually in young individuals, prone to attacks of paroxysmal tachycardia, which is in rare instances on the basis of paroxysmal auricular fibrillation.

4. The etiology is entirely unknown.

5. In certain cases atropine and exercise will abolish the block temporarily, but there are too many examples which do not respond to these stimuli adequately to substantiate the theory that the phenomenon is entirely the result of excess vagal tone.

6. The diagnosis can be made by the electrocardiogram, for in no other condition is bundle branch block associated with a short $P–R$ interval.

7. The disorder apparently has no pathologic significance, and does not in any way shorten the life span of the individual.

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CRITERIA OF OXYGEN WANT, WITH ESPECIAL REFERENCE TO NEUROCIRCULATORY ASTHENIA.

By F. K. Hick, M.D.,

ASSOCIATE IN MEDICINE; ASSOCIATE ATTENDING PHYSICIAN, RESEARCH AND EDUCATIONAL HOSPITAL, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL,

A. W. Christian, M.D.,

FORMER RESIDENT IN MEDICINE, RESEARCH AND EDUCATIONAL HOSPITAL, CHICAGO, ILLINOIS,

AND

P. W. Smith, Ph.D.,

ASSOCIATE IN PHYSIOLOGY, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL.

We are accustomed to recognize anoxemia by the presence of symptoms. Particularly cyanosis has long directed attention to poor oxygenation of the blood. More recently (Waters[10]) much of the knowledge of symptoms of oxygen want has been organized so as to be of ready aid in diagnosis of anoxemia in cases where it is known to be a possible development, as in pneumonia, chest injuries, congestive heart failure, and so on.

However, objective criteria of oxygen want are too few, and if they could be worked out would help in the recognition of borderline anoxemia situations whose frequency and importance are now unknown.[3]

The best method for determining an oxygen lack due to faulty aeration of blood passing through the lungs is the analysis of arterial blood. This technique was introduced by Hürter.[6] The application of analysis of arterial blood has been greatly facilitated by Van Slyke's development of his manometric gas analysis apparatus. Stadie,[9] and others, with this apparatus have recorded low oxygen saturation results in pneumonia, heart disease, asthma and pulmonary fibrosis. Only a few normal subjects have been so studied,[4] not enough to permit statistical determination of the normal, or a definition of a borderline range of saturation between clear-cut normals and clear-cut anoxemic individuals. The 16 normal sub-

jects we studied showed no evidence of any disorder of the cardio-respiratory mechanism. However, several came below the figure of 95% which is held to be "normal." In 16 normals so studied the arterial oxygen saturation ranged from 98.8 to 93.4%, with a mean of 95.6%. In 38 cases in the literature the range was from 93.2 to 100%, with a mean of 95.7%.

Since many conditions of anoxia are peripheral in type (*i. e.*, properly aerated arterial blood moves so slowly through the peripheral capillary bed that it is reduced in oxygen content below the optimum for tissue nutrition), the study of arterial blood should be supplemented by less direct methods which would show lack of adequate supply of oxygen to the tissues. Determination of venous lactic acid, together with a shift in this figure when oxygen is respired, might constitute evidence of oxygen want. The idea is based on observations of Hill,[5] *in re* oxygen debt. We also attempted a second procedure aimed at detecting lack of oxygen on the following reasoning: If a patient is suffering from oxygen want, breathing oxygen instead of air should significantly alter the rate of oxygen consumption. Determination of tissue gas tension and of alveolar CO_2 was abandoned for various technical reasons as unsuited for this purpose.

Therefore, we adopted the plan of recording degree of oxygen saturation of arterial blood, along with venous lactic acid before and after breathing oxygen, and also determined the oxygen consumption of patients breathing air and breathing oxygen according to the following routine:

Methods. The brachial or femoral artery was punctured by passing a 20-gauge needle on a syringe containing novocaine through a novocaine wheal. This needle was slowly advanced, while novocaine was infiltrated, into the artery. Once the blood was flowing the syringe was changed for an oiled syringe containing a bit of powdered buffered oxalate and mercury (for mixing). Using an eccentric tip syringe it was easy to draw the blood without contact with air and store it in the syringe until ready for analysis. The oxygen content was regularly determined in duplicate on 2-cc. samples, using the manometric apparatus and standard technique.[8] The oxygen capacity was similarly done after aerating a part of the same sample.

Oxygen consumption (breathing air and oxygen) was done as follows. The patient at basal conditions first had a basal rate taken by the Tissot tank method while breathing air. The samples were analyzed either by a Haldane or a Van Slyke apparatus by standard methods. After 5 to 8 minutes' rest this was repeated, using a Benedict-Roth machine rebreathing oxygen through soda lime. After another 3 to 5-minute interval the Tissot was repeated and finally the fourth determination of the morning was made by the Benedict-Roth apparatus.

The lactic acid determinations were made by the method of Friedman, Cotonio and Shafer.[1] The blood was drawn without stasis from the same cubital vein before and after rebreathing oxygen from a Benedict-Roth apparatus with the subject at basal conditions.

Results. The results of these 3 procedures on cases with clear-cut oxygen want are shown in Table 1. In cases having low arterial

oxygen saturation and hence an anoxemia the lactic acid shift was usually absent, even though a shift of 1 mg.% was considered significant. These low lactic acid figures are explained by the patients being at basal conditions. However the "basal by 2 methods" procedure shows one or the other or both Tissot results lower than the Benedict-Roth average results. Where the data are inconsistent, they are recorded ±. The shift in the *R.Q.* was a rise of over 0.05 after breathing oxygen and could best be explained by the theory that an oxygen want was present, but was made good by breathing oxygen and afterward the oxygen "debt" reappeared when air was breathed. If there had been no interval this effect would result from the residual air in the lungs becoming almost pure oxygen and hence giving a low oxygen absorption and a high *R.Q.* in the second Tissot. The timing of the routine precluded this error.

TABLE 1.—RESULTS ON DECOMPENSATED ORGANIC HEART DISEASE.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid.	Second lactic acid.	Shift.	Initial Tissot low.	Second Tissot low.	Shift in R.Q.
K.	82.0	7.4	5.9	Yes	±	±	±
D.	88.4	....	....	....	+	+	+
Go.	....	10.6	10.2	No	±	+	+
Ga.	94.0	....	....	....	±	+	+
U.	92.0	....	....	....	+	±	+
Wo.	96.4	10.4 10.4	10.6 9.6	No	+	+	+
Sc.	95.4	7.4 9.4	6.7 9.2	No	−	+	+
Wa.	93.8	....	....	....	+	±	+
St.	92.3	10.7 13.3	9.6 11.4	Yes	±	+	+
Wau.	92.0	7.5	8.9	No	−	+	+

The control group of healthy people are tabulated in Table 2. Where arterial puncture was not done there was no reason to suspect a low result.

TABLE 2.—NORMALS.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid.	Second lactic acid.	Shift.	Initial Tissot low.	Second Tissot low.	Shift in R.Q.
B.	96.4	7.4	6.5	No	−	−	−
St.	94.0	...	...	...	−	−	−
Lo.	93.5	...	...	...	−	−	−
Sm.	....	...	...	...	−	−	−
Sl.	....	7.0	7.2	No	−	−	−
		8.1	7.4	No	−	−	−
La.	....	8.5	8.0	No	−	−	−
Le.	....	9.0	8.3	No	−	−	−
G.	....	6.5	6.9	No	−	−	−

The striking results in a few neurocirculatory asthenia cases were not entirely foreseen. Table 3 lists the arterial oxygen saturation in several neurocirculatory asthenia cases who showed the symptoms described by Lewis[7] and by White.[11] Undoubtedly in certain severe cases a true anoxemia exists. That in less severe cases an anoxemia

also is present is indicated by the results in Table 3 where again + signs predominate in the 3 columns to the right.

TABLE 3.—RESULTS ON NEUROSIS CASES.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid	Second lactic acid	Shift.	Initial Tissot low.	Second Tissot low.	Shift in R.Q.
C. . .	78 83 91	16.7	7.7	Yes	+	+	+
		18.2	14.0				
B. . .	83 86	16.2	13.5	Yes	±	+	+
		6.5	5.2				
F. . .	84	10.7	10.6	No	±	+	+
		7.4	7.4				
S. . .	85.6	....	....	...	+	+	+
W. . .	89.5	....	....	...	+	+	+
H. . .	92 93	13.7	8.0	Yes	±	±	±
	90 97	20.2	12.2				
		8.7	6.7				
		9.6	7.6				

In considering the reason for faulty aeration of blood passing through normal lungs we thought of possible "shunts" from pulmonary artery to vein, and shallow breathing, and marginal atelectasis. Greene[2] suggested that anoxemia could result with the chest in an expanded position, *i. e.*, an increased residual air, and a normal tidal air which would for that individual at the moment be an inadequate ventilation.

An interesting side issue was the observation that in any of these anoxemia situations elevated basal rates resulted on breathing oxygen, as though an oxygen debt were being made good. The clinical application of this fact must be of aid in the distinction of any anoxia from true elevations of B.M.R. This fact may help in the differential diagnosis of neurocirculatory asthenia and hyperthyroidism.

Summary. Neurocirculatory asthenia showed in 13 cases an inadequate arterialization of blood leaving the lungs. These patients also showed other indirect evidence of oxygen want in that the *R.Q.* and oxygen consumption altered with the patient breathing oxygen. These latter changes were regularly found in decompensated organic heart disease cases. Such findings support the opinion of Haldane that part of the symptoms of these patients are from anoxemia, especially the respiratory irregularities. These patients often present difficulty in differential diagnosis from hyperthyroidism, therefore a watch for evidence of oxygen want may bring certain B.M.R. results into suspicion of artificial elevation.

Conclusions. 1. The above criteria are definite evidence of oxygen want and together indicate whether it is pulmonary or peripheral in type.

2. Oxygen saturation of less than 94% appears insufficient optimally to supply the organism with oxygen, so that the "borderline" group having oxygen saturations of 90 to 94% are really in anoxia.

3. Neurocirculatory asthenia is featured by an oxygen want of pulmonary origin, present in certain patients. Anoxemia probably contributes to the fatigue of these patients and accounts for certain other symptoms.

4. An anoxic situation can give elevated basal metabolic rate results, if taken from oxygen-rebreathing apparatus.

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THE EFFECT OF LIVER EXTRACT ON THE ABSORPTION OF FAT IN SPRUE.

By W. Halsey Barker, M.D.,

ASSISTANT IN MEDICINE, ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH,

AND

C. P. Rhoads, M.D.,

ASSOCIATE MEMBER, ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK.

(From the Hospital of the Rockefeller Institute for Medical Research.)

A DISTURBANCE of the absorption of fat from the intestinal tracts of patients with sprue has been assumed to exist almost since the recognition of the disease. The belief in the existence of such a disorder of fat absorption has been based upon the presence of large amounts of fat in the feces of the patient with sprue during the acute phase of the disease and upon the absence of excess fat during clinical remissions.

Previous studies of the fat content of the feces of patients with sprue have indicated that it is largely split and that hence the disorder is not one of pancreatic function (Fairley[2]). It has not been clear, however, whether the diarrhea which is so frequently a symptom of sprue caused the malabsorption of fat or whether the presence of unabsorbed but split fat caused the diarrhea. No proof has been advanced furthermore that the fat in the intestine has not been absorbed and subsequently excreted.

Castle, Rhoads, Lawson, and Payne[1] described the improvement

of the intestinal symptoms of patients with sprue which follows the suitable administration of liver extract. Mackie, Miller, and Rhoads[4] demonstrated characteristic alterations of intestinal motility and outline by Roentgen ray examination, and Miller and Rhoads[6] showed in one case that these alterations were less pronounced after liver extract had been injected and symptoms had disappeared.

This communication reports a study of the amount of fat which is present in the blood of normal subjects following the taking of a meal rich in fat, and compares the results with those in patients during exacerbations of the diarrhea of tropical sprue as well as during the remissions which follow the administration of liver extract.

Methods. The method employed for the determination of the blood lipids was that described by Kirk, Page and Van Slyke.[3] Heparin was employed as an anticoagulant. The subjects fasted overnight and a sample of blood was taken before the test meal of fat. Samples of blood were withdrawn at 2, 4, and 6 hours after the ingestion of the fat. The meal was composed of heavy cream and butter in the ratio of roughly 6 to 1 with a small amount of bread as a vehicle for the butter. In the early experiments, the patients took 4 gm. of fat per kilo of body weight, but such a large amount of fat proved rather difficult to tolerate and in later studies the amount was reduced to 2 gm. per kilo. This decrease in the fat content of the meal seemed to occasion but slight variation in the results. Little discomfort resulted from the test, although in the subsequent 48 hours several bulky loose stools were frequently passed, particularly in cases during relapse. Diarrhea occurred in no case while absorption was being studied and when samples of blood were being withdrawn. The low concentration of fat could not be ascribed therefore simply to rapid loss of the administered fat from the intestinal tract. The time relationship between the intake of fat and defecation suggested strongly that malabsorption caused the abnormal stools rather than the reverse.

In the early experiments total lipid carbon, total lipid cholesterol, and lipid phosphorus were all determined. After repeated studies had shown that little or no change in the levels of free and of total lipid cholesterol occurred after the fat meal, these determinations were discontinued.

Results. As a preliminary study the amounts of lipid in the blood of 4 normal individuals before and after taking a fat meal were measured by the Kirk method. Previous studies on normal controls had employed techniques which differed from each other so considerably that the results are not comparable either with each other or with our findings.

The results are reasonably constant; Figures 1 and 2 and the fasting levels of total lipid carbon were uniformly in the range between 320 and 480 mg. %. The peak of the rise was reached at the end of 4 hours and the maximum level attained was between 550 and 650 mg. %. Free and total lipid cholesterol levels failed to show consistent changes, although they tended to rise slightly. Lipid phosphorus levels rose not more than 2 mg. % but were consistently increased. Following the maximum levels a gradual decrease tended to occur but in all instances the lipid content at the end of 6 hours was greater than the fasting level.

The results obtained from the study of the normal individuals were in agreement with those reported by Kirk, Page and Van Slyke on

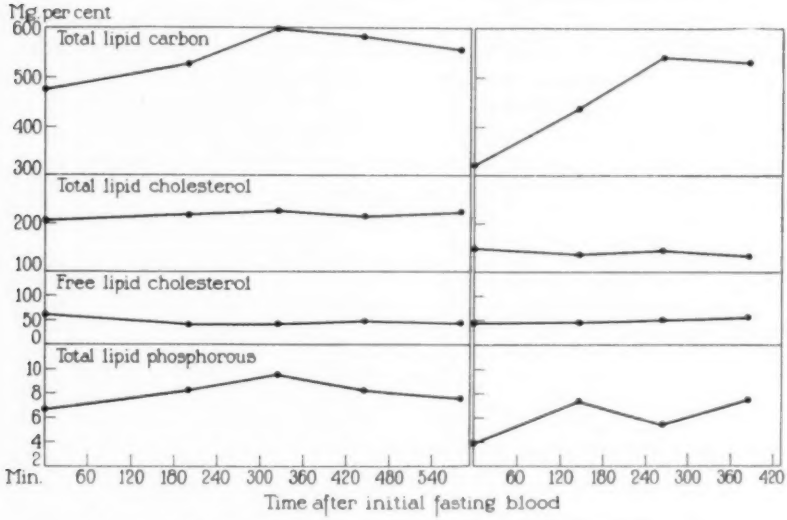
Mg. per cent
Total lipid carbon
Total lipid cholesterol
Free lipid cholesterol
Total lipid phosphorous
Min.
60 120 180 240 300 360 420 480 540
60 120 180 240 300 360 420
Time after initial fasting blood

FIG. 1.—Blood-lipid patterns in 2 normal individuals following fat meal.

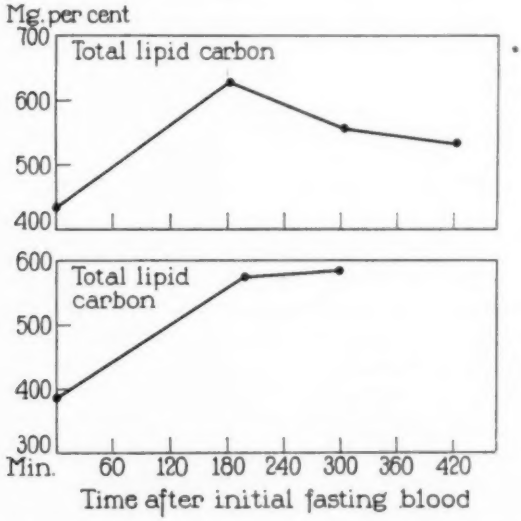

FIG. 2.—Total lipid-carbon curves of 2 normal individuals following fat meal.

fasting men and by Man and Gildea[5] after a fat meal, although the latter workers employed a somewhat different analytical procedure.

After the amounts of lipid in the blood of normal subjects had been ascertained for the fasting state and after eating a meal of fat, 3 cases of sprue were studied before and after treatment with liver extract, and 2 more cases before but not after treatment. All 5 were cases of typical sprue, acquired in the tropics and of long duration. All had suffered from macrocytic anemia and stomatitis at

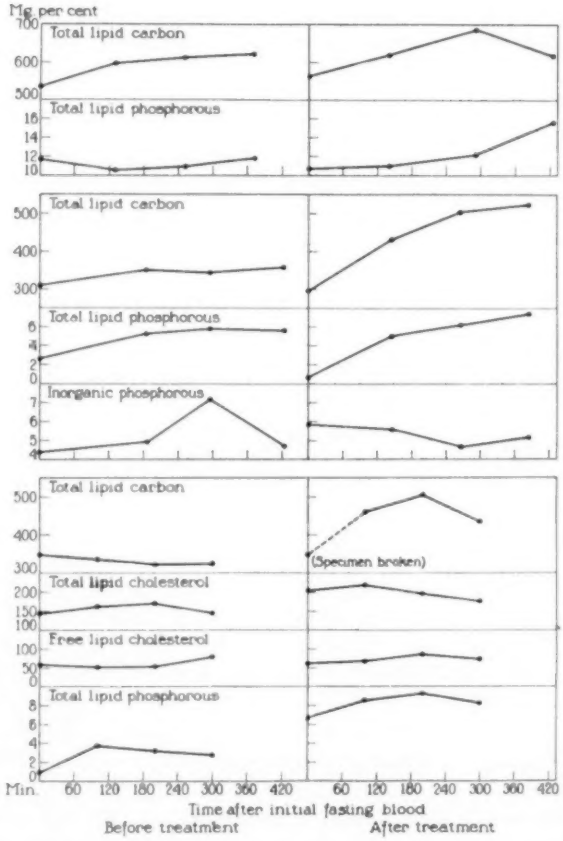

FIG. 3.—Blood-lipid patterns in 3 sprue patients following fat meal. On the left, the curves before liver-extract treatment; on the right, the curves following treatment.

one time, but when tested neither hematologic nor oral symptoms were prominent. Abdominal distention, gas, and bulky, soft, gray stools were distressing features and were characteristic of the disease.

During a preliminary period of not less than 4 weeks all the sprue patients tested were given a diet which contained almost no fat and limited carbohydrates, but which was rich in its content of

proteins and fresh fruit, a diet widely accepted in the treatment of sprue. During this control period the intake of fat was made constant before the test was made. In no instance were the patients symptom-free on this régime, although all were considerably better than was the case when a general diet containing lipid was taken.

The amounts of lipid in the blood of all 5 cases of sprue showed practically no increase following the fat meal (Figs. 3, 4). This fact, coupled with the well known observation that a large amount of fat is present in the intestinal contents, seems to be adequate evidence that the absorption of fat is interfered with in the active phases of the disease even though anemia and stomatitis are not present.

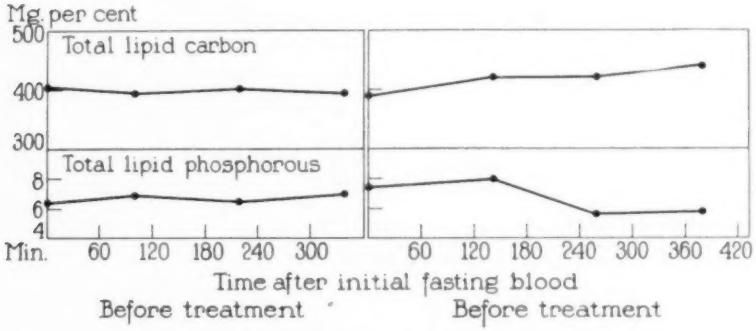

FIG. 4.—Blood-lipid curves of 2 sprue patients following fat meal before liver-extract treatment.

The 3 cases which were tested again after treatment with liver extract injected intramuscularly showed wholly different amounts of lipid in the blood. All clinical symptoms were then quiescent. In Case 2 one injection of liver extract (10 cc. Lilly N.N.R., derived from 50 gm. of liver) was sufficient, whereas in the other cases several injections repeated daily were required. In all 3 cases a pronounced rise in the level of the total lipid carbon resulted, and the resultant curve approached normal in both duration and height, presenting a striking contrast to the practically flat curves obtained before treatment.

Discussion. From the results which have been presented it seems to be clear that normal individuals react to a meal containing 2 gm. of fat per kilo of body weight by a pronounced and well sustained increase of the amounts of lipid in the blood. Patients with sprue, on the other hand, still manifesting symptoms after treatment with diets low in the content of fat, exhibit no such increase under similar experimental conditions. If treatment with liver extract, parenterally administered, is instituted, however, amelioration of symptoms results and a normal increase in the levels of lipids in the blood fol-

lows the taking of the same amount of fat, which was ingested previously.

The passage of bulky loose stools follows the taking of a test meal of fat before treatment with liver extract, but this does not occur during the 6-hour period of the test, but only from 12 to 48 hours after the experiment has been terminated. This time relationship of diarrhea to the withdrawal of blood samples for analysis suggests that the lack of increase of the content of the blood lipid cannot be ascribed to loss of fat from the intestinal canal, but to an actual failure of absorption by the intestinal mucosa. It is to be inferred from this observation that malabsorption results in diarrhea rather than that diarrhea is the cause of malabsorption. This conclusion is substantiated by the fact that diarrhea ceases on the parenteral administration of liver extract and is associated with normal amounts of lipid in the blood after the taking of a meal of fat. This observation suggests not only that remissions in sprue are associated with return of normal absorption of fat, but also that liver extract exerts some specific effect in converting malabsorbing intestines to normal function. It might be supposed that improvement was due to some alteration in bile salts, were it nor for the observation of Thaysen[5] that the bile salt content of the duodenal contents is perfectly normal in patients with sprue.

Thaysen has administered bile salts furthermore to such patients without affecting the excretion of fat, while Starr and Gardner[7] found no decrease of the fat excretion of patients with sprue during the oral administration of bile. Although the effect of liver extract in promoting absorption from the intestinal tract in patients with sprue requires further investigation, it seems probable that the effect is a direct one upon the intestinal wall. This assumption is strengthened by the report of Fairley that the absorption of sugar from the intestinal tract is subnormal in such cases during relapse but improves after treatment. Unfortunately, his cases are not strictly comparable to ours for they were treated by a combination of restricted diet and liver extract orally administered, so that the effect due to either diet or liver extract alone cannot be estimated. Our cases were followed on the usual régime of restricted fat and carbohydrate intake sufficiently long to establish the facts that the absorption of fat was below normal on such régimes and that it was improved by the injection of liver extract.

Conclusions. 1. The levels of fat in the blood after the ingestion of a meal rich in fat have been determined for normal subjects by the method of Kirk, Page and Van Slyke.

2. Five cases of sprue studied during the presence of intestinal symptoms showed an absence of the normal increase in the levels of fat in the blood after a fat meal.

3. Three of the 5 cases were tested after the parenteral adminis-

tration of liver extract and showed postabsorptive levels of fat in the blood which approached the normal.

4. The experimental results suggest that in sprue, liver extract exerts some specific effect upon the absorptive power of the intestinal tract.

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PROTAMINE INSULINATE IN THE TREATMENT OF DIABETES IN PSYCHOTIC PATIENTS.

By Joseph M. Looney, M.D.,
DIRECTOR OF LABORATORIES, WORCESTER STATE HOSPITAL,
AND
W. Everett Glass, M.D.,
CHIEF PHYSICIAN, MEDICAL AND SURGICAL SERVICE, WORCESTER STATE HOSPITAL, WORCESTER, MASS.

(From the Memorial Foundation for Neuro-endocrine Research and the Medical and Surgical Service, Worcester State Hospital.)

The treatment of diabetes in psychotic patients offers many problems that are not found in the usual diabetic clinics of the general hospital.

These patients are frequently uncoöperative and almost without exception are prone to pilfer food. Many times they strenuously object to being given their injections so that the excitement aroused by this procedure three times a day serves to elevate their blood sugar levels still further. For these reasons the charts of the diabetic patients show great fluctuations in blood sugar levels and urinary sugar excretion. When the laboratory reports a very high blood sugar level, the insulin may be increased in an effort to reduce it, and subsequently a dangerously low level may result. Any method which can reduce the number of injections required and afford a continuous supply of insulin throughout the day would be particularly beneficial in the treatment of these patients. This seems to have been accomplished by the use of protamine compounds of insulin by Hagedorn and his co-workers.[3a]

The new compound and its zinc modification have been studied by various investigators (Hagedorn,[3b] Joslin,[4] Joslin, *et al.*,[5] Rabinowitch, *et al.*,[6,7] Root, *et al.*,[10] Sprague, *et al.*,[11] Campbell, *et al.*,[2] Richardson and Bowie[9]). The beneficial effects and the decrease in both number of injections and total amount of insulin needed seem

to be firmly established by their work. Certain precautions against overdosage and the insidiousness of hypoglycemic symptoms have been emphasized by Allen.[1] Richardson[8] has described the advantages of protamine zinc insulin and given detailed directions for its use.

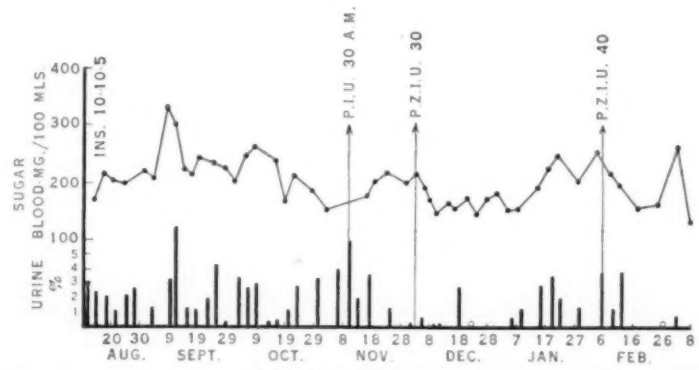

CHART I.—J. P., age, 58; weight, 185; duration, 8 years; diet, C. 200; P., 180; F., 100; D. P., hebephrenic.

Since August, 1936, we have been utilizing various preparations of Protamine Insulinate and Protamine Zinc Insulinate* in the treatment of 4 diabetic male patients. A single injection was given before breakfast and the diet was evenly distributed through the three meals. A brief clinical account of each patient follows:

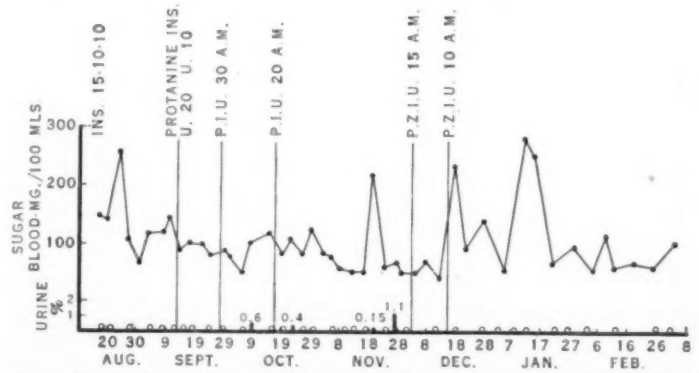

CHART II.—O. C., age, 66; weight, 112; duration, 9 years; diet, C. 138; P., 78; F., 138; PSY., with psychopathic personality.

Case Abstracts. CASE 1.—O. C., male, white, aged 66, was admitted to this hospital March, 1915. Diagnosis: psychosis with psychopathic personality. He also had syphilis and was given antiluetic treatment. He was first noticed to have diabetes and moderately advanced pulmonary tuberculosis in 1932. Physical examination revealed moderate peripheral

* This material was supplied through the courtesy of Eli Lilly & Co.

arteriosclerosis with blood pressure of 128/92. The urine contained sugar and the blood sugar was elevated. He was put on a diabetic diet of carbohydrates 138, protein 78, fat 138, and insulin 15–10–10 units. Considerable difficulty was experienced in controlling the diabetes because of the patient's

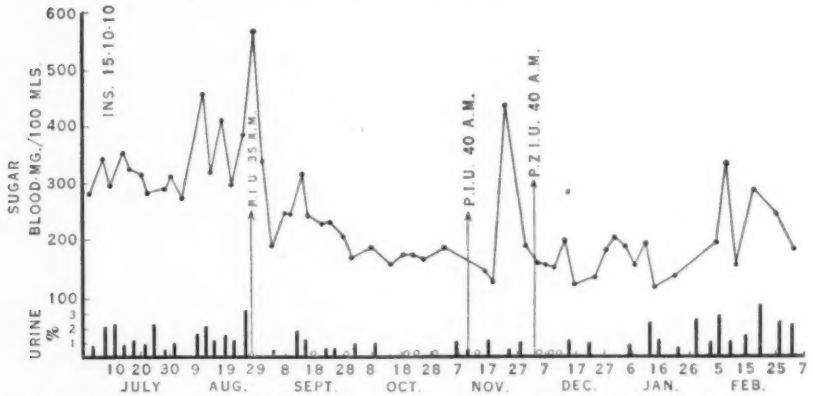

CHART III.—R. K., age, 58; weight, 160; duration, 6 years +; diet, C. 200; P. 60; F. 100; general paresis.

uncoöperativeness in taking food from other patients' trays. His blood sugar varied from 80 to 250. The urinary sugar varied from zero to 0.6%. September 15, 1936, he was started on protamine insulinate, 30 units daily. The blood sugar gradually became lower and showed much less fluctuation. On November 25 insulin was cut to 15 units and on December 15, 1936, to 10 units daily. Except for an occasional fluctuation the blood sugar is now between 70 and 100 and urine is sugar-free.

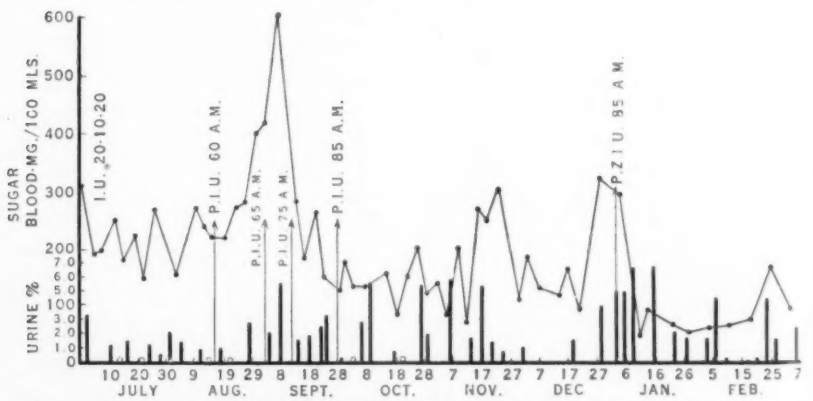

CHART IV.—J. S., age, 50; weight, 133; duration, 9 years; diet, C. 150; P., 70; F., 100; D. P., paranoid.

CASE 2.—J. P., male, aged 58, admitted to this hospital July, 1921, was diagnosed as a case of dementia præcox, hebephrenic type. He was first noticed to have diabetes in 1929, with sugar in his urine and blood sugar elevated. Physical examination showed heart and lungs to be normal and

blood pressure 150/90. On a diet of carbohydrates 200, protein 80, fat 100 and insulin 10–10–5 units, the blood sugar fluctuated from 150 to 325 and the urine contained from 1% to 10% sugar. The patient was uncoöperative, stealing food from other patients. On November 10, 1936, he was placed on protamine insulin, 30 units, and the same diet followed. The blood sugar showed less fluctuation, varying from 150 to 210. On December 1, 1936, protamine zinc insulin was started and for 1 month the blood sugar remained between 150 to 160, then the sugar began to rise to 250. Protamine zinc insulin increased to 40 units February 6, 1937. The blood sugar is still fluctuating, but is tending to return to a normal level.

Case 3.—R. K., male, white, aged 50, was admitted to this hospital October, 1931, because of dementia paralytica and diabetes mellitus. Physical examination showed moderate peripheral sclerosis, blood pressure 150/90, heart and lungs normal, pupils not reactive to light. The blood and spinal fluid gave positive Wassermann reactions for which he received antiluetic treatment. On a diet of carbohydrates 200, protein 60, fat 100, with insulin 15–10–10 units, the diabetes was very difficult to control. Blood sugar varied from 260 to 564 and urine at times contained as much as 3% sugar. In August, 1936, the patient developed a cellulitis of the left leg and a beginning gangrene of the left heel. He was placed on protamine insulinate, 35 units in A.M., on August 27, 1936. The blood sugar went steadily to 160 and the condition of the leg improved. On November 10, 1936, protamine insulinate was increased to 40 units. Protamine zinc insulin was started on December 3, 1936. Blood sugar after this was consistently below 200 until February, 1937, when the patient was allowed off Medical Service. Since then the blood sugar has again become irregular, varying from 150 to 320 and the urine contains from 1 to 3% sugar. This variation is due undoubtedly to the patient's taking food from other trays.

Case 4.—J. S., male, white, aged 50, was admitted to this hospital March, 1919. Diagnosis: dementia præcox, paranoid type. He was first discovered to be a diabetic in 1929. Physical examination showed that the heart and lungs were normal and blood pressure 136/88. He was placed on a diet of carbohydrates 150, protein 70, fat 100, with insulin 20–15–20 units. The blood sugar varied from 310 to 250 and urine sugar from zero to 3.5%. Protamine insulinate was started August 16, 1936, 60 units in A.M. The blood sugar showed a steady climb, reaching a height of 600. The insulin was increased up to 75 units, when blood sugar began to come down, and on September 28, 1936, 85 units were given daily. Blood sugar on this dosage became fairly stable around 150, but urine still contained from 3% to 6% sugar. On January 3, 1937, protamine zinc insulin was started, 85 units in A.M., and the blood sugar became much lower, all figures being below 100. In spite of this low blood sugar, the urine still contained from 2% to 4% sugar.

Discussion. In one case a smaller dosage of insulin was accompanied by a lower blood sugar level; in the other 3 the dosage of protamine insulinate was increased above that of unmodified insulin, but the fluctuations in blood sugar were markedly diminished. In one patient, J. S., in whom the excretion of sugar continued even though the blood sugar level fell well below the normal value of 100 mg. %, an abnormally low sugar threshold appeared to be responsible. In his case the change to protamine zinc insulinate was definitely of value, as for the first time consistently low values were obtained for his blood sugar.

The use of protamine zinc insulinate was admittedly subjected

to a very severe test in these 4 cases. In 2, the diabetes was associated with lues; one also with tuberculosis. In all cases a definite improvement in the physical condition of the patients was seen, and a decrease in the marked fluctuations in the blood sugar levels.

On the basis of these experiments it has been decided to extend the use of the protamine zinc insulin to all diabetics requiring more than a single injection of unmodified insulin to control their blood sugar level, as the slow release of insulin is able to compensate for the uncoöperativeness of the patients with respect to diet.

Summary.—Four diabetic psychotic male patients were treated with protamine insulinate and protamine zinc insulinate. It was found that this treatment was more satisfactory than the use of regular unmodified insulin, resulting in a decrease in the fluctuations in blood sugar levels and in one case in a reduction of insulin requirements from 35 to 10 units daily.

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CORONARY THROMBOSIS WITHOUT PAIN.

By Linn J. Boyd, M.D., F.A.C.P.,

PROFESSOR OF MEDICINE, THE NEW YORK MEDICAL COLLEGE AND FLOWER HOSPITAL,

AND

S. Charles Werblow, M.D.,

RESIDENT ON MEDICINE, THE NEW YORK MEDICAL COLLEGE AND FLOWER HOSPITAL, NEW YORK CITY.

(From the Department of Medicine, The New York Medical College and Flower Hospital and the Metropolitan Hospital.)

Practically all discussions of the clinical features of coronary artery disease have cardiac pain as their central theme. This emphasis, entirely justified, has created coronary artery-consciousness so that occlusion of these vessels, formerly often overlooked because of atypical pain, at present may be diagnosed when other painful syndromes are actually present. But in both situations it is pain which plays the leading rôle.

Evidence is rapidly accumulating to show that coronary thrombosis may occur without pain; in fact, qualified observers have suggested that painless coronary episodes are about as frequent as the

dramatic painful accidents. These estimates, based upon post-mortem material, contain an obvious source of error, namely many patients are too ill to permit detailed inquiry and the record may be inadequate on the subject of pain. Nevertheless painless coronary thrombosis must be fairly common, since one-third of our patients with proven coronary thrombosis manifested no pain, although this point was the subject of particular interrogation in the last 127 cases coming under our observation. This percentage excludes patients whose condition did not permit a detailed history to be taken. In view of the frequency of coronary thrombosis, this aspect of the subject would seem to have been neglected if brevity of discussion in monographs and paucity of the reported instances in medical literature may be employed as criteria.

The purpose of this paper is not to report hitherto unknown facts but to direct attention to an apparently common but seemingly neglected aspect of an important problem. Seven cases of this nature, reported as briefly as possible, have been selected to illustrate some of the clinical pictures encountered.

Clinical Abstract. CASE 1.—A. W., a 61-year-old Jewish male salesman was admitted for convalescent care on February 5, 1937. On August 6, 1936, he was seen at an allied hospital because of an attack of "asthma" of a few hours' duration. For a few weeks prior to the attack there had been exertion dyspnea, occasional nocturnal dyspnea and slight ankle edema; otherwise he had been well. A diagnosis of coronary thrombosis was made upon electrocardiographic evidence and he remained in the hospital for 6 weeks because of dyspnea, orthopnea and malleolar edema. Gradual improvement occurred and he was discharged to a convalescent home. After some time the symptoms reappeared, requiring re-hospitalization; upon improvement he was transferred to Metropolitan Hospital. He stated that he had never experienced any precordial, abdominal, neck or arm pain and that he had not had any gastro-intestinal disturbances. At this time he was free from dyspnea although some nocturnal distress had been present for 3 nights prior to admission.

Examination revealed a fairly well-developed and well-nourished male lying flat in bed. There was no dyspnea, cyanosis or edema. The neck veins were not distended. The left border of the heart was 2 cm. beyond the nipple line and the cardiac sounds were distant. A soft systolic murmur was heard at the apex and transmission to the axilla noted; a few premature contractions were observed. The lungs and abdomen were negative, the extremities free from edema; the brachial vessels were thickened. Blood pressure, 100/56; temperature, 98.6° F.; pulse, 80. The blood Wassermann reaction was negative and the blood chemistry normal. The urine contained a trace of albumin and a few hyaline casts; the specific gravity was 1.018. Sedimentation of the red blood cells 1 mm./hr.; leukocytes numbered 6900. The electrocardiogram on admission is reproduced in Figure 1.

On January 23 at 8 P.M. he suddenly became very dyspneic and weak following an attempt to defecate. His face was pale, the expression apprehensive, the lips cyanotic and there was marked orthopnea. The neck veins were distended. No pain experienced. Blood pressure, 60/30 (?), rate rapid but regular; heart sounds of poor quality, very distant and a suggestion of gallop rhythm. Râles were noted at the bases of the lungs.

On the next day the liver was palpable 3 fingers below the costal margin and edema of the legs had appeared. Blood pressure, 60/?. The tem-

perature was 102° F.; leukocytes numbered 16,800 with 82% neutrophils; sedimentation time, 64 mm./hr. The electrocardiogram now showed a radical change. The presence of a Q wave in L_1 and small upward deflection, prominent S wave in L_2 and deep S wave in L_3 and the absence of definite bundle-branch block (QRS interval, 0.10) suggest myocardial infarction in the territory of the anterior coronary artery (Fig. 2). The patient went steadily downhill and died, January 25, 1937.

Autopsy Extract. "The heart and aorta weighed 1050 gm. The epicardium was markedly infiltrated with fat, the coronary vessels somewhat tortuous. On the posterior aspect of the left ventricle there is a slight deposit of fibrin. An area of softening, about the size of a dime is seen midway between the base and apex, about 1 cm. from the interventricular groove. The myocardium of the right ventricle is 5 mm. in thickness, the pulmonary valve normal. The intima of the pulmonary artery is normal except for patches showing hemolysis. The myocardium of the left ventricle is 1.5 cm. in thickness. There is slight hardening of the base of the aortic ring. The coronary orifices were normal. The thoracic aorta revealed some lipoidal infiltration and scattered atheromatous plaques. Among the trabecula of the left ventricle there are some adherent thrombi. The mitral valve is normal. The right auricular appendage is empty.

"On section the myocardium has a decidedly pale, parboiled appearance. An area of softening corresponding to the area mentioned on the posterior aspect of the left ventricle extends into the myocardium. The coronary arteries are sclerotic, but an actual thrombus was not observed. The anatomical diagnosis was coronary thrombosis, myocardial infarction, thromboendocarditis, aortic and renal arteriosclerosis."

Comment. An elderly male was observed during two episodes of myocardial infarction. A completely negative past history suggests that he belonged to the group of so-called "latent coronary artery disease." His first major coronary accident was not associated with pain but with an equivalent in the form of "asthma" superimposed upon mild cardiac failure. The second episode followed slight exertion and was likewise free from pain; otherwise the symptomatology was not unusual.

CASE 2.—P. E. (No. 437), a 77-year-old white female, entered the hospital, March 16, 1936. For the past 3 years she had experienced dyspnea on exertion and occasionally at rest; transient edema of the ankles and rare attacks of nocturnal orthopnea developed at the same time. She emphasized that these attacks were always painless, occurred after exertion and consisted of "gasping for air and much sweating." She also had noted attacks of vertigo and black spots before the eyes. In 1934, she was hospitalized for dyspnea and discharged improved; at that time she was informed of the existence of hypertension. More recently there has been nocturia and increased urinary frequency during the day. Very recently her vision has been failing. Throughout the past year she has attended cardiac clinic. The night before admission she suddenly became dyspneic and was compelled to gasp for air. The difficulty persisted and she called an ambulance the following morning.

Examination revealed an elderly white female, markedly dyspneic and orthopneic. The fundi showed tortuous and narrowed arteries. The neck veins were distended. Moist râles were heard over both bases. The blood pressure was 190/110. The heart was enlarged to the left and a rough systolic murmur was audible over the entire precordium, loudest at the apex. The pulmonic second sound was accentuated; heart sounds of fair

quality, rate 108. The peripheral vessels were sclerotic. The liver edge was felt 2 fingers below the costal margin. The extremities showed a few varicosities and no edema. She was regarded provisionally as an instance of "arteriosclerotic heart disease with marked left- and mild right-sided failure with passive congestion" and treated accordingly.

On the day after admission the temperature rose to 101° F. and remained somewhat elevated for the next 10 days; dyspnea and orthopnea gradually increased, more râles were noted in both lung fields, peripheral edema increased. On March 28 she became mentally confused and remained so until death, on April 16. The blood pressure was variable, usually somewhat lower than on admission, once rising to 200/135 and near the end approximating 155/90. The blood Wassermann reaction was 1+, the blood chemistry normal; the urine revealed a trace of albumin and a few granular casts. Concentration tests showed a fixation of specific gravity between 1.016 and 1.018. The white blood cell counts averaged 14,000, with 84% neutrophils. The sedimentation times were 40 mm./hr. (March 17) and 90 mm./hr. (April 9).

On March 16 the electrocardiogram was as follows: rate 104, L.A.D. T_1 diphasic. P–R interval 0.20; March 20, the rate 78, L.A.D., P–R interval 0.24. L_1 and L_2 S–T depressed. P waves very small in L_1, L_2, L_3. The change was regarded as due to digitalis.

At *autopsy* the heart and aorta weighed 620 gm. The aortic ring revealed marked hardening and the aorta showed many atheromatous patches. The coronary vessels were decidedly sclerotic, tortuous, but patent except the left descending branch which was obliterated. On section, the myocardium, in the area supplied by the left descending branch, shows an extensive whitish patch with transverse striations. Microscopic examination revealed a healing infarct of the myocardium.

Comment. An elderly female with known hypertension, arteriosclerotic heart disease, mild congestive and left ventricular failure entered the hospital for relief of dyspnea. Similar episodes had occurred before, but this time the attack persisted. There was no pain, the blood pressure did not fall, but the sedimentation velocity had increased. The electrocardiogram presented changes compatible with known prolonged administration of digitalis. During her brief hospitalization the passive congestion increased and the picture suggested a terminal bronchopneumonia superimposed upon hypostasis. Postmortem examination revealed coronary thrombosis, myocardial infarction (healing stage), and passive congestion of the lungs.

In retrospect it has seemed to the writers that coronary infarction occurring in the course of congestive failure is often not associated with pain. It is generally known that the pain of "angina pectoris" tends to disappear when congestive failure occurs, but it does not seem equally widely appreciated that pain may not be present even when major coronary artery accidents occur during congestive failure.

CASE 3.—A. M. (No. 984), a white Italian female of 70, entered the hospital, November 19, 1936. For the last 7 years she has had exertion dyspnea but no symptoms when at rest. Intermittent edema of the ankles has been present during the same period. No precordial pain has ever been present; hypertension has existed for several years. About 2 weeks

before admission the dyspnea became decidedly worse, marked orthopnea developed and ankle edema increased.

The patient was an elderly white, markedly dyspneic and orthopneic female. Cyanosis of the lips and nose noted. Bilateral cataracts exist. There was decided fullness of the neck veins. Impaired resonance over both lung bases and moist râles in the same areas. Blood pressure 138/78, rate rapid. The heart sounds are hardly audible owing to the chest noises. The pulse was weak in quality and irregular in rhythm. The peripheral vessels were sclerotic. The liver edge was palpable 2 fingers below the costal margin and tender. Marked pitting edema of the lower extremities up to the knees.

The temperature was normal on admission but it rose to 100° F. later in the day, to 101° F. on the following day and 100° F. on the third, the day of her death. The pulse ranged between 100 and 120. Sedimentation 90 mm./hr. On the second day the blood pressure fell to 88/46 and she lapsed into coma from which she did not recover. The electrocardiogram briefly was as follows: normal sinus rhythm, rate 108. *P–R* interval 0.20. No axis deviation. *QRS* complexes very small in all leads. *P* and *T* waves also very small in all leads.

Autopsy. The heart weighed 450 gm. "Within the left ventricle at the apex there is a very soft thrombus adherent to the wall. When the thrombus was removed, the myocardium appeared to bulge, not unlike a cardiac aneurysm. At the center of the bulging area, the myocardium is about 1 mm. thick. The myocardial softening extends a short distance beyond the area occupied by the thrombus. The mouths of the coronary vessels are narrowed and the vessels are sclerotic. At 2 cm. from the origin of the left descending coronary artery the lumen is obstructed by a recently formed thrombus. The aorta shows many calcified plaques." (For microscopic report see later.)

Comment. As in the preceding case the correct antemortem diagnosis was not established. In retrospect coronary thrombosis ought to have been considered in view of our inability to explain satisfactorily the sudden aggravation of her symptoms. It is also of interest to note that 3 of the cases reported here are elderly hypertensive females. In our experience, Cases 2 and 3 represent the most common syndrome of "painless" coronary thrombosis, namely, unexplained aggravation of dyspnea occurring during the course of congestive heart failure.

CASE 4.—M. R. (No. 987), a white female dressmaker, aged 55, was admitted to the hospital, November 15, 1935, at 1 P.M. As she was in coma no history could be obtained. The landlady who accompanied her stated that the patient had been found lying unconscious on the floor of her room. A few hours earlier the patient had seemed to be entirely well and no outcry had been heard in the adjoining room.

The patient was an emaciated comatose white female. The cheeks were ashen, the lips and fingers cyanotic, the extremities cold and covered with clammy perspiration. Temperature normal; pulse, 110; respirations, 24; blood pressure, 110/70. No marks of violence on the body and no evidence of skull injury. The pupils were slightly contracted and reacted poorly to light and accommodation. No odor to the breath. The neck veins were distended. Auscultation of the lungs revealed numerous fine moist râles throughout the lower two-thirds of both lungs. The left border of the heart was 3 cm. beyond the nipple line; the heart sounds were poor in quality and the first sound roughened at the apex; occasional premature con-

tractions. Moderate sclerosis of the brachial vessels and a few varicosities of the lower extremities were recorded. The abdomen was negative. Since she was found in collapse without a history of previous illness, her appearance, rapid pulse, weak heart sounds, a diagnosis of coronary thrombosis was suggested and corresponding therapy initiated. Later in the day she improved considerably. She stated that she had been feeling perfectly well, had suddenly become dizzy, and "must have lost consciousness." Several years ago she had been informed of the existence of hypertension and during the last 2 years had experienced several attacks of precordial pain. For the last year she had suffered from numerous headaches, occasional attacks of vertigo, exertion dyspnea and insomnia. That night the cyanosis diminished and her color improved. The blood pressure remained unchanged. The white blood cell count was 10,500 with 77% neutrophils; the red blood cells numbered 4,440,000; sedimentation time 1 mm./15 min. A friction rub was now audible in the third left interspace over the precordium. As the electrocardiograph was out of order, no tracing was secured. The next morning her condition became poor. The pulse was rapid and weak and she died at 8 A.M., about 30 hours after admission.

Autopsy. The epicardium showed abundant fat. The mitral, pulmonary and tricuspid valves were normal; some sclerosis at the base of the aortic valve. The left ventricle measured less than 1 cm. in thickness At the apex it was somewhat thinner, very flabby, and covered by a thick layer of fat. On section, the myocardium showed a large patch with whitish striations, this patch being paler and softer in consistency than the remainder of the myocardium; the corresponding layer of endocardium had lost its luster. The coronary arteries were markedly sclerotic; the anterior branch of the left descending artery was occluded by a thrombus; the smaller branches were sclerotic and obliterated.

Comment. Several cases of this type could have been included. In some there is sudden marked vertigo followed by extreme weakness. As in the other cases no history of pain could be obtained at the time of the illness.

CASE 5.—P. F. (No. 1030), a 53-year-old white laborer, entered the hospital, October 28, 1936. Two hours before admission while sitting in his room he suddenly experienced marked breathlessness, weakness and then fainted. He recovered consciousness in a few minutes and noticed, in addition to breathlessness, that he was bathed in cold perspiration. He felt very apprehensive and weak. There was no pain but decided palpitation: "the heart was fluttering." Slight nausea followed. He informed the ambulance physician that the fluttering had diminished but the weakness and breathlessness persisted: "I feel as if I were suffocating." Two years before admission he had been informed of the existence of hypertension and had sought medical aid for "attacks of fluttering in the heart" which appeared on exertion. There had never been any edema, nocturnal dyspnea nor gastro-intestinal complaints. No further history was attempted because of his poor condition but detailed inquiry on the subject of pain failed to elicit any presence of this symptom.

Examination revealed an obese white male with marked respiratory distress and orthopnea. The face was ashen, lips and extremities cyanotic. He appeared apprehensive and answered questions in a weak, husky voice. The neck veins were distended. The lower two-thirds of both lungs were filled with moist râles. The heart was enlarged to the left and the sounds of poor quality, "tick-tock rhythm." The rate was rapid and the heart irregular. No murmurs were detected. The abdomen was soft and the liver just palpable. No clubbing or edema of the extremities but defi-

nite coldness and cyanosis. Temperature, 97° F.; pulse, about 160; respiration, 38; blood pressure, 125/100. The probable diagnosis seemed coronary thrombosis; an immediate electrocardiogram revealed auricular fibrillation; ventricular rate, 150. *QRS* of marked amplitude in L_2 and L_3. Ventricular premature contractions. Slight depression of *S–T* segment in L_1, high take-off of *S–T* segment in L_2 and L_3. One hour after admission the blood pressure was 70/? and 30 minutes later the patient was dead.

Owing to the fact that the patient had recently participated in a fight, the body was sent to the Medical Examiner. A telephonic report informed us that a fresh thrombosis was found in the posterior descending artery.

Comment. This patient, like the preceding, gave a history of hypertension and he had been cardiac conscious for 2 years. Exclusive of the absence of pain, he presented the usual features of coronary thrombosis.

Case 6.—B. J. (No. 208), a 62-year-old colored laborer, entered the hospital, February 5, 1937. In 1929, he noted dyspnea on exertion and shortly afterwards orthopnea, nocturnal dyspnea, and slight edema of the extremities. These symptoms appeared intermittently and improvement coincided with visits to a dispensary. Several years ago as well as 2 months before hospitalization he was informed of the existence of hypertension. In 1935, he was hospitalized for decompensation and about that time he complained of slight precordial pain, radiating to the left shoulder which lasted for a few minutes. It was not severe and never recurred. Three weeks ago he had a slight "cold." Otherwise the history is negative, in fact, it was singularly free from previous illnesses, although hemorrhoids were present for a short time several years ago. He is the son of a white father and a half-white mother. The night before hospitalization, just before retiring, he experienced a sudden severe choking sensation in the throat together with marked weakness, faintness and dyspnea. This persisted through most of the night, gradually diminishing in severity. There was no associated pain.

The examination revealed a well-developed, somewhat undernourished, elderly, light colored negro who was markedly dyspneic and orthopneic. The neck veins were distended and the chest emphysematous. Moist râles were heard throughout both lung bases. Blood pressure, 130/90. The left border of the heart was in the anterior axillary line, sounds distant. There was normal sinus rhythm and a short harsh systolic murmur was heard at the apex. The brachial vessels were sclerotic. The liver edge was palpable 3 fingers below the costal margin. No edema or clubbing of the extremities. A few external hemorrhoids were noted.

The electrocardiogram on admission is shown in Figure 3, and 3 days later (February 8) in Figure 4. On February 15: *P–R* interval, 0.22. Deep *Q* wave in L_2; definite *W*-shape of *QRS* in L_3; *S–T* rounded and high take-off in L_2, L_3. L_3, absence of initial downward deflection.

The diagnosis of acute coronary occlusion was made on the basis of acute onset, relatively low blood pressure and the electrocardiographic findings. He improved somewhat during the first few days, but then dyspnea and orthopnea increased, edema of the extremities developed, additional râles in the lungs were evident. He went steadily downhill and died 19 days after admission. No autopsy was permitted.

Extracts from the laboratory and other reports follow: On admission: temperature, 97° F.; pulse, 100; respiration, 30. On the following day the temperature rose to 101° F., then down to 100° F. for 1 week and then normal. The pulse was constantly about 100. The initial blood pressure

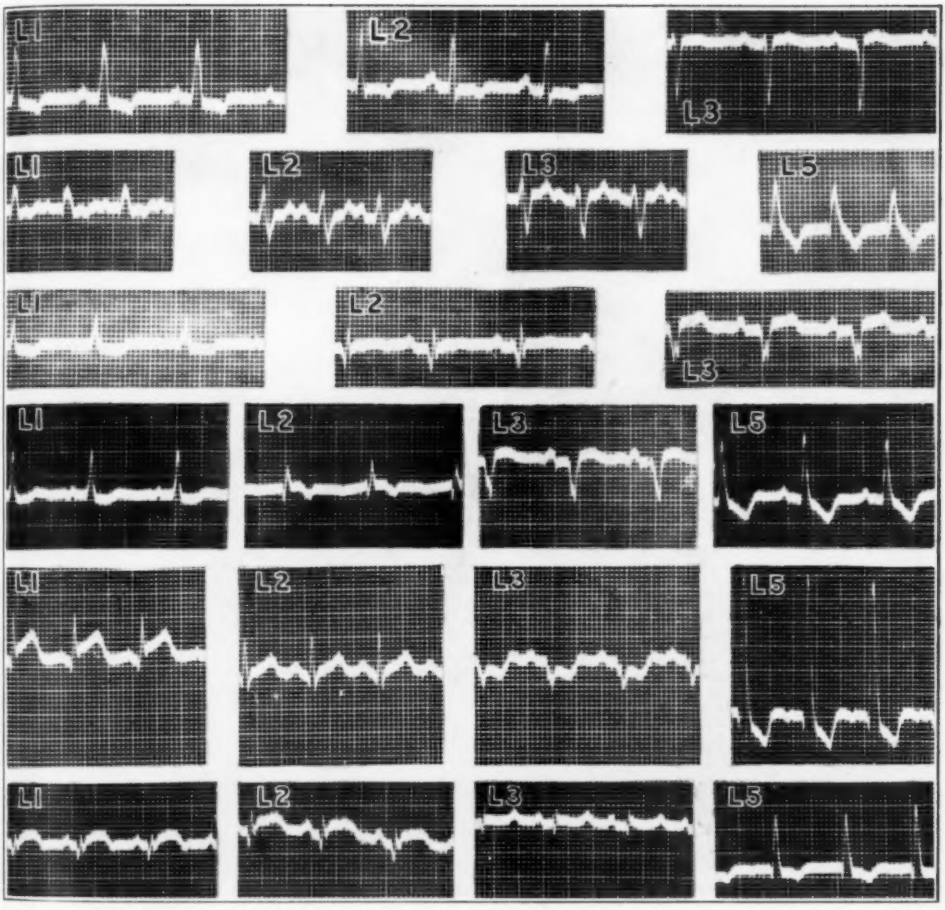

Fig. 1.—Case A. W. (December 20, 1936.) Electrocardiogram shows regular sinus rhythm 80/min. S–T_1 and S–T_2 segments slightly depressed, S–T_3 rounded. T_1 inverted and T_2 coved.

Fig. 2.—Case A. W. (January 23, 1937.) Electrocardiogram shows sinus tachycardia rate 130/min. QRS complexes small; P–R interval 0.20 Q_1 present; S_2 and S_3 prominent; T_1 diphasic. In L_5 initial downward deflection very small.

Fig. 3.—Case B. J. (February 5, 1937.) The electrocardiogram shows normal sinus rhythm, rate 88/min. P–R interval 0.20; QRS small; tendency to "W" shaped Q in L_3. S–T_1 depressed and slightly elevated take-off of S–T_3. T_1 diphasic and T_2 almost isoelectric.

Fig. 4.—Case B. J. (February 8, 1937.) Electrocardiogram shows definite Q_2. S–T_3 segment rounded. In L_5 initial downward deflection absent.

Fig. 5.—Case H. P. (October 28, 1936.) Electrocardiogram shows normal sinus rhythm, rate 109/min. High take-off of S–T_1, with large T wave. S–T_2 slightly elevated. Markedly depression of S–T_3. In L_5 the initial downward deflection is very small.

Fig. 6.—Case H. P. (November 4, 1936.) Electrocardiogram shows QRS complexes small in all leads. In L_1 and L_2 S–T segment rounded with a high take-off and S–T_3 almost isoelectric. T_3 small and upright. In L_5 initial downward deflection is very small and upward deflection is smaller than previous E.C.G. (Fig. 5) and T wave is isoelectric.

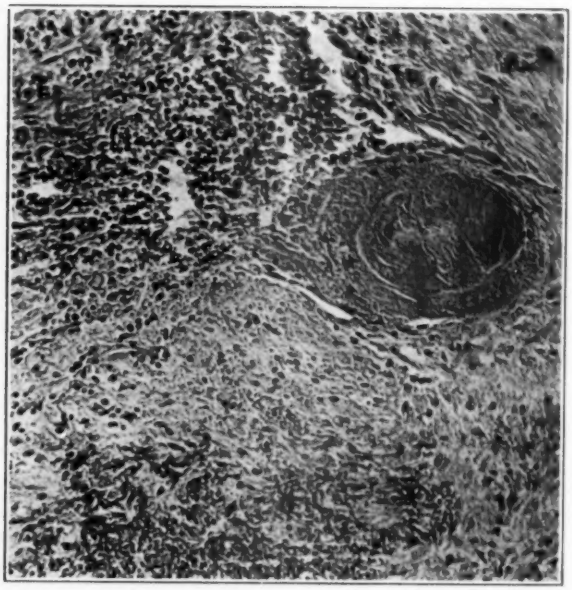

FIG. 7.—Myocardial infarction. Case 3. Vascular thrombosis, proliferating fibrous tissue, focal cellular infiltration (lymphocytes and monocytes), coagulative necrosis with hemorrhage.

fell to 120/75 on the day after admission and then returned to its initial level and remained so until death. The blood chemistry was normal, the urine showed a trace of albumin. The white blood cells were 22,400, with 76% neutrophils. Sedimentation times: February 8, 42 mm./hr.; February 15, 80 mm./hr.; February 17, 62 mm./hr. Roentgen ray of the chest showed cardiac enlargement and pulmonary congestion.

Comment. The patient, a known hypertensive cardiac, experienced sudden severe choking as an equivalent of cardiac pain; this was followed by dyspnea and cardiac failure in which previous exertion did not play a rôle. Except for the absence of pain the patient presented many of the usual features of coronary thrombosis.

Case 7.—H. P. (No. 1058), a 51-year-old white male factory worker, entered the hospital, October 28, 1936. One hour before admission, shortly after eating lunch, he suddenly experienced great weakness and faintness. He sat down in order to avoid falling. He felt nauseated and then vomited several times; profuse perspiration then developed. On admission he still complained of weakness, nausea and vertigo and stated that he "was frightened about himself." He was emphatic on the point that there had not been any pain in the chest, abdomen, neck, or arms and that he had never experienced abdominal or "hunger" pains. On rare occasions during the past few years he has had slight vertigo and mild exertion dyspnea. (Several days later on further inquiry he admitted that there had been occasional "heaviness" of the chest when he exerted himself extremely, but he had not given this any attention.) The past history was negative. His father died of a "stroke" and his mother of "acute indigestion."

The examination revealed a somewhat obese, well-developed white male who seemed apprehensive and who answered questions in a weak voice. Temperature, 97° F.; pulse, 120; respirations, 24. The face was pale and the lips cyanotic. The pupils were equal and reacted to light and accommodation. Blood pressure, 160/110. The left border of the heart was 3 cm. outside the nipple line; the heart sounds were fair in quality; no murmurs; the aortic second sound slightly accentuated. A few râles were noted at the right base. The abdomen was flat, no rigidity or masses; slight tenderness and slight resistance of the upper abdomen. The remainder of the examination was negative.

Perforated peripyloric ulcer or coronary thrombosis seemed to be the probable diagnosis. An electrocardiogram taken immediately revealed changes typical of anterior coronary occlusion (Fig. 5). The white blood cell count was 7800, the sedimentation time 17 mm./hr. One hour after admission the blood pressure was 130/95; 3 hours, 100/70; 5 hours, 100/70.

He was treated as a coronary thrombosis and by evening was quite comfortable except for gradually developing dyspnea and orthopnea. Slight nausea persisted. On the following day he vomited once. The weakness persisted, dyspnea and orthopnea diminished. Râles could be heard over both bases. Blood Wassermann test negative. A trace of sugar was found in the urine and this persisted for 3 days (the admission specimen was free from sugar). Blood sugar: 125 mg. per 100 cc.; November 3, blood sugar, 260; November 6, 220 mg. per 100 cc.

On the second day a friction rub was detected over the precordium. The white cells had increased to 18,250 and the sedimentation was now 38 mm./hr., temperature 101° F. and the blood pressure 112/72. There was gradual improvement except for vomiting when he ate more than a few mouthfuls of food. On November 3: temperature, 100° F.; pulse, 100; blood pressure, 130/90; white blood cells, 17,600; sedimentation, 90 mm./hr.

The basal râles persisted. The electrocardiogram of November 4 is shown in Figure 6. On November 7, no change was noted in the electrocardiogram. The sedimentation time was now 102 mm./hr. Early the morning of November 8 he mentioned mild aching in both shoulders. Two hours later he was found dead in bed. Except for this aching his history was devoid of pain. An autopsy could not be obtained.

Comment. This case was selected to illustrate the so-called "digestive group;" in this patient the symptoms resembled those encountered in an abdominal lesion, for example, atypical ruptured ulcer.

Since this paper is intended to emphasize some of the common clinical features of "painless" coronary artery disease, detailed comment upon the subject of cardiac pain is not relevant. However, attention may be momentarily directed toward one aspect of the pathologic physiology of the situation.

Unfortunately our past records are not sufficiently complete for ascertaining whether or not the cases reported belong to Libman's hyposensitive group. The existence of individuals hyposensitive to pain seems unquestionable. However, this theory was probably never intended to represent a complete explanation for absence of pain in coronary thrombosis. On the other hand, it is generally known that destruction of the vessels, nerves and functioning muscular tissue, renders an area insensitive so that painful responses are not experienced when new obstruction develops. For this reason it would seem reasonable to assume that in some cases the absence of pain in coronary artery disease could be explained upon the basis that the infarction occurs into a "dead" area. This seemed to have occurred in the third case reported. The microphotograph is taken from nearby areas of the myocardium (Fig. 7). The picture strongly suggests that the infarction occurred into a fibrotic area.*

The detailed description of the microscopic sections of Case 3 follows. It should be noted that the second paragraph of the description arises from other sections than those depicted here.

Case 3 (Cont'd).—"Microscopic section of the heart shows a myocardial layer of varying thickness distorted by rather extensive chronic degenerative necrosing and productive changes. Large areas of cardiac muscle fibers are in advanced states of hyalin and granular coagulative necrosis. Throughout this necrotic tissue varying amounts of actively proliferating fibrocapillary tissue is seen. Focal areas of lymphocytic, plasma cell and mononuclear cell infiltration are common. Many of the large mononuclear cells have brownish pigment granules in their cytoplasm and are probably indicative of previous hemorrhage. Free masses of yellowish-brown pigment are also noted throughout the developing connective tissue. Subjacent to the necrotic endocardial tissue is a thick layer of proliferating fibrovascular tissue in which there are several large areas of coagulative

* We are indebted to Dr. Francis D. Speer for the description of the microscopic sections. The extracts from autopsy protocols in the above reported cases are available through the courtesy of Dr. Andrea Saccone.

and lytic necrosis with somewhat recent hemorrhage. A large fibrinocellular thrombus is attached to the necrotic endocardial tissues. A fragment of papillary muscle shows extensive muscular cytonecrosis and active fibrous tissue proliferation. In the fibrofatty subepicardial tissue there is one moderate sized transected coronary vessel in the media of which definite hyalin changes are seen.

"Another section shows a large branch of a coronary vessel with an irregularly thickened wall and a lumen reduced to about 30% of its normal size. The lumen contains a small amount of eosinophilic material and a few poorly preserved red cells. The lining endothelium is intact but shows small amounts of attached granular and fibrinous material. The intima is thickened and shows a variety of necrosing, fibrosing and calcific changes. An occasional distorted fragment of the internal elastic membrane can be identified. The muscular layer is very thin and shows poorly stained atrophic smooth muscle fibers. Throughout the myocardium of this section there is a fine fibrillar fibrosis often taking the form of small stellate shaped scars. Focal areas of muscular cytonecrosis are often in or near these fibrotic areas.

"*Pathological Diagnoses.* Advanced coronary atherosclerosis with calcification. Marked cardial infarct showing advanced muscular necrosis and active organization with old and recent hemorrhage into the area of infarction. Intracardial fibrinocellular thrombosis."

The absence of pain in myocardial infarction has been explained by the assumption of the extravasation of blood into a fibrotic area. Stated in this manner, the explanation seems applicable in only 1 of the cases reported above. Further light has been thrown upon this question by animal experimentation, particularly by the work of Katz. If the nerve plexus surrounding a coronary vessel is destroyed by phenol, compression of the artery does not induce responses which are considered identical with pain; however, the response is not abolished when an area above the phenolized vessel is stimulated. The part played by the nerve plexus in coronary pain will be the subject of a future communication.

Summary. Additional evidence is submitted to support the idea that major coronary thrombosis may occur without pain. Pain was not present in one-third of 127 cases of coronary thrombosis observed by the writers during a 25-month period, although its occurrence was the subject of particular inquiry.

Seven cases of this type are reported briefly. The occurrence of 3 female cases among 7 reports is suggestive of the increasing occurrence of coronary thrombosis in women. Although Metropolitan Hospital has a large negro clientele, only 1 colored patient is reported and he was the son of a white father and half-white mother.

Most of the cases were known cardiacs and had manifested more or less cardiac failure for periods varying from a few weeks to many years. Sudden inexplicable increased congestive failure in a known cardiac should arouse suspicion of coronary thrombosis; moreover in such cases pain is usually absent. We had 1 case of a pain equivalent in the form of "choking," several of severe vertigo,

commonly associated with periods of unconsciousness, and 1 of a painless episode in the so-called "digestive" group.

The diagnosis of painless coronary thrombosis, as a rule, should not be difficult if the possibility is considered. Our mistakes have occurred mainly in elderly individuals with known arteriosclerotic heart disease and hypertension.

Painless coronary thrombosis probably occurs more frequently than is generally appreciated and we may assume that mild cases are more common than the fatal examples reported in this paper.

As the histories of these cases are singularly free from pain, they may belong to Libman's hyposensitive group. It is suggested that greater attention should be paid to the nerve plexuses surrounding the coronary vessels in cases of painless coronary infarction.

CEREBRAL EMBOLISM AS A COMPLICATION OF CORONARY THROMBOSIS.*

By Daniel L. Dozzi, M.D.,

ASSISTANT PHYSICIAN, CHESTNUT HILL HOSPITAL; CLINICAL ASSISTANT, GRADUATE HOSPITAL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(Under the Diagnostic Hospital Endowment Fund of the Graduate School of Medicine.)

Levine[5a] has made the statement, "When a sudden hemiplegia occurs in a patient whose blood pressure is not remarkably elevated, the diagnosis of cerebral hemorrhage is too often made. In some cases of this type, the hemiplegia is due to an embolus and not to a hemorrhage and more careful search for data pointing to coronary thrombosis should be made." At even an earlier date, Cabot[2] had made similar remarks.

Interest in this subject was stimulated by the repeated emphasis of Levine[5b] that emboli from cases of coronary thrombosis might explain some of the obscure hemiplegias and also because of observing at autopsy a case with an antemortem diagnosis of cerebral hemorrhage, which created no particular curiosity in itself, but later caused considerable excitement upon discovery of a rather extensive, unpresumed myocardial infarct with mural thrombi and the brain apparently the site of an embolus.

The literature failed to exhibit studies presenting the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of either cerebral hemorrhage or cerebral thrombosis. Consequently, to determine the true incidence of cerebral embolism as a sequel of coronary thrombosis one must not concentrate attention wholly upon those cases known to have coronary thrombosis.

* Part of thesis which was submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc.(Med.)) for graduate work in internal medicine. Presented (by invitation) before the Section on General Medicine of the College of Physicians of Philadelphia on May 24, 1937.

Analysis of 138 Consecutive Brain Examinations. Because of the observation that coronary thrombosis might be entirely unindicated in some of the hemiplegics, 1000 consecutive, unselected autopsies* were studied from the standpoint of the relationship between cerebral lesions and coronary thrombosis. Of the 1000 cases, there were 138 whose brains were examined at autopsy. Hemiplegia or hemiparesis was responsible for examination of the brain in 99 cases (on the left side in 46, on the right in 39, and bilateral in 4). Hemiparesis was reported on the left side in 9, and on the right side in 6.

TABLE 1.—THE INDICATION FOR BRAIN EXAMINATION.

Chief neurological sign or symptom leading to brain examination.	No. of cases.	% of the total.
Hemiplegia (recent)	65	47.1
Hemiplegia (old and recent)	15	10.8
Hemiplegia (became unconscious)	9	6.5
Hemiparesis	10	7.2
Weakness or paralysis of one or more extremity	10	7.2
Unconscious (sudden)	7	5.0
Severe headache	4	2.9
Aphasia	3	2.1
Dizziness	2	1.4
Blindness	2	1.4
Delirium	3	2.1
Skull fracture	1	0.7
Spastic quadriplegia	1	0.7
Bell's palsy	1	0.7
Meningismus	1	0.7
Sudden death after thoracocentesis	1	0.7
Change in personality	1	0.7
Became confused	2	1.4
Total	138	

TABLE 2.—CHIEF FINDING AT AUTOPSY.

	No. of cases.		% of the total.
Cerebral thrombosis	77		55.8
Cerebral hemorrhage	25		18.1
Thrombosis and hemorrhage	4	106	2.9
Meningitis (2 miliary abscess)	5		3.6
Marked cerebral arteriosclerosis	4		2.9
Subdural hemorrhage	3		2.1
Edema and congestion	3		2.1
Old cortical scars	2		1.4
Tuberculoma	2		1.4
Abscess	2		1.4
Glioma	2		1.4
Metastatic carcinoma	1		0.7
Fibroblastoma	1		0.7
Extradural hemorrhage	1		0.7
Cerebral atrophy (idiot)	1		0.7
Multiple sclerosis and old hemorrhage	1		0.7
Subarachnoid hemorrhage	1		0.7
Meningovascular syphilis	1		0.7
Cerebral thrombosis and myomalacia of cord	1		0.7
Embolism	1		
Total	138		

* From the files of the Phila. Gen. Hosp. Laboratories; acknowledgment is hereby made to the members of the laboratory staff for permission to use this material.

Table 2, which shows the chief pathologic lesion of each brain, reveals that cerebral thrombosis was present in 77, hemorrhage in 25, both thrombosis and hemorrhage in 4, and embolism in 1. The group comprised of thrombosis, hemorrhage, thrombosis and hemorrhage, and embolism accounted for 107 (77.5%) of the cerebral lesions. One is impressed with the scarcity of embolism but upon investigation it appears to be not a question of scarcity as much as difficulty in differentiating embolism from thrombosis. Dr. Riggs,[8*] who examined practically all of these brains, thinks it possible that some of the cases listed under cerebral thrombosis may be cerebral embolism; however, in some instances she found it impossible to make the differentiation.

In addition to the above cases that had the brain examined at autopsy, there were 29 that had definite clinical evidence of a cerebral lesion, but unfortunately the brain was not examined at autopsy. These cases, presented in Table 3, were not included with

TABLE 3.—CLINICAL NEUROLOGICAL SIGN OR SYMPTOM.

	No. of cases.
Hemiplegia (Right, 9; Left, 10)	19
Hemiparesis (right)	2
Unconscious (sudden)	2
Speech difficulty, 1 arm weak	1
One arm flaccid	1
Twitching right side of body	1
Paralysis left arm and leg	1
Meningeal irritation	2
Total	29

the original 138 that were specifically examined for cerebral lesion, because the clinical picture might strongly suggest a cerebral lesion and yet the autopsy might only show cerebral arteriosclerosis, or congestion and edema, as was the case in 7 of the 128 cases whose brains were actually autopsied.

A word is needed here on the use of the term coronary thrombosis. Boyd properly warns against employing the term coronary thrombosis synonymously with myocardial infarct, for he points out that the latter might be due to causes other than coronary thrombosis. Nevertheless, since the terms were often used interchangeably in the pathologic descriptions, they are similarly used here.

Analysis of Patients with Coronary Thrombosis. Of the 1000 cases studied, all had both gross and microscopic examination of the heart. In this group, there were 41 cases with established coronary thrombosis. Twelve of the 41 cases (29%) were associated with either cerebral thrombosis or cerebral embolism. These figures differ decidedly from those in the literature.

Conner and Holt,[3] in reviewing 287 cases with coronary throm-

* Chief, Division Neuropathology, Laboratories, Phila. Gen. Hosp.

bosis, state that 14 had developed cerebral embolism and 2 exemplified cerebral thrombosis many months after the attack of coronary thrombosis. In this series, approximately 5% of the patients with coronary thrombosis developed cerebral embolism.

TABLE 4.—ANALYSIS OF 41 PATIENTS WITH CORONARY THROMBOSIS.

	Age.			Sex.		Color.	
	20–39.	40–59.	60–79.	Female.	Male.	White.	Colored.
Coronary thrombosis and/or myocardial infarct*	5	21	15	16	25	25	16
Above cases complicated by cerebral thrombosis or cerebral embolism	3	5	4	2	10	10	2

* Of the 41 cases with coronary thrombosis, 4 occurred in syphilitic heart disease, 2 in rheumatic heart disease and the remainder in either arteriosclerotic heart disease or normal hearts.

Parkinson *et al.*[7] refer to embolism as a complication of coronary thrombosis and of 83 cases autopsied, found cerebral embolism in 1 (an incidence 1.2%).

Meakins and Eakins[6] report the autopsy findings of 62 cases with coronary occlusion and state that 6.4% had a cerebral thrombosis.

From the above studies, one readily observes that there is considerable variation in the occurrence of cerebral embolism in cases with coronary thrombosis. One will also notice a marked difference between the above reports and the present study. The 12 cases presented in this study having both a cerebral lesion and a coronary thrombosis had a clinical diagnosis of either cerebral hemorrhage or cerebral thrombosis. The cardiac lesion in all but 2 was unexpectedly found at autopsy. In these two exceptions the suspicion of coronary thrombosis was aroused, but the diagnosis was not definitely established. These cases would not have been discovered had they been studied from the aspect of cerebral embolism in cases with coronary thrombosis.

Of the 41 cases with coronary thrombosis, 29 had a clinical diagnosis corresponding to the pathologic finding. The additional 12 cases of coronary thrombosis were found indirectly by determining the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage or cerebral thrombosis.

In Table 3, 29 cases are presented showing clinical evidence of a cerebral lesion, but the brain was not examined at autopsy. Two of these cases had coronary thrombosis which was also recognized clinically. From the latter group, wherein only the hearts were examined, one notes that the occurrence of associated cerebral embolism and coronary thrombosis is not as high as in the group where the brains as well as the hearts were examined at autopsy. Incidentally, the brains were not routinely examined in the studies reported by Connor and Holt,[3] Parkinson *et al.*,[7] and Meakins and Eakins.[6] If we could feel justified in assuming that each of the 29 cases with neurologic manifestations but no brain examination had

a definite cerebral lesion of the nature of a thrombus or an embolus, then we could say that of the 29 cases with coronary thrombosis recognized clinically (from the group of 41) there were 2 (6.9%) that were complicated by either cerebral thrombosis or embolism. This latter figure would compare favorably with the reports of the above authors.

Coronary Thrombosis Often Unsuspected in Presence of Cerebral Lesion. While it appears that investigators are quite aware of cerebral embolism as a complication of coronary thrombosis, they are not so alert in recognizing the condition when the coronary thrombosis is not obvious and the first symptoms are those of embolism. Table 4 would also indicate that the white male of 40 or over is the most prone to develop cerebral embolism as a complication of coronary thrombosis.

If this high incidence of cerebral thrombosis or embolism in patients with coronary thrombosis can be substantiated, it seems that we have not been sufficiently aroused by the previously mentioned warning of Levine,[5a] even though some of these cases were admitted to the neurologic service in stupor thereby making it impractical to obtain accurate information concerning previous history. Some of these cases had complained of either substernal pain, epigastric pain, arm pain, or neck pain 6 to 8 weeks prior to the onset of hemiplegia. These probably were some of the atypical forms of coronary thrombosis.

It is well known that one may have a painless coronary thrombosis. East *et al.*,[4] as well as many others, have called attention to this fact. Parkinson[7] says that dyspnea may replace and take the part of pain if infarction is superimposed on preëxisting signs of heart failure. Painless coronary thrombosis, as well as other atypical forms, might assist in explaining why the coronary thrombosis is not always suspected. It is also possible that cerebral thrombosis might be merely coincidental to the fall in blood pressure which frequently accompanies coronary thrombosis. The clinical picture of cerebral thrombosis thereby masking the cardiac lesion.

In the analysis of 138 brain examinations of which 12 cases (8.6%) also had coronary thrombosis, let it be recalled that the diagnosis of coronary thrombosis was not given in a single case and suspected in only 2. Excluding those cases whose brains showed glioma, fibroblastoma, tuberculoma, and so on and considering only those cerebral lesions which might have some relation to the events which follow coronary thrombosis (cerebral hemorrhage, cerebral thrombosis and cerebral embolism) we could then say that the incidence would be 12 out of 107 (11.2%) which had a cerebral thrombosis associated with coronary thrombosis. Analogous figures of other writers are not given because no similar studies were found.

A study is now being conducted to determine clinically the occur-

rence of coronary thrombosis in cases with a clinical picture of a cerebrovascular lesion.

Summary and Comment. One thousand consecutive, unselected autopsies were analyzed for the incidence of cerebral embolism and cerebral thrombosis in cases known to have coronary thrombosis. The same series was then analyzed for the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage, cerebral thrombosis and cerebral embolism.

Of the 1000 cases, there were 138 whose brains were examined at autopsy. Of these, 107 had either cerebral hemorrhage, cerebral thrombosis or cerebral embolism. Of these 107 there were 12 cases (11.2%) that also had coronary thrombosis. The latter lesion was not diagnosed clinically in a single case and suspected in only 2.

While there were 41 cases of coronary thrombosis in the series of 1000 autopsies, only 29 of these were clinically recognized and recorded. The remaining 12 were found as clinically unsuspected coronary thromboses in the autopsy records of the 107 cases that had a clinical diagnosis of either cerebral hemorrhage, cerebral thrombosis or cerebral embolism. None of the 29 cases clinically recognized was shown to be associated with a cerebral lesion. The association of 12 of the 41 cases of coronary thrombosis with a cerebral vascular lesion gives an incidence of 29%, a higher figure than those found in the literature.

Though this series is too small to permit definite conclusions, this indication of a high incidence of unsuspected coronary thrombosis in cases of hemiplegia should serve as a stimulus for more extensive study and investigation.

As a result of the findings of this study, the following suggestions present themselves:

1. While it is generally felt that the heart is frequently the source of a cerebral embolus in persons below 40 years, it would be wise to suspect the heart in all cases of cerebral embolism, irrespective of the patient's age.

2. When suspecting the possibility of coronary thrombosis as the etiologic factor in a case of hemiplegia, we must bear in mind the atypical forms of coronary thrombosis and must not lose sight of the fact that in cases with congestive heart failure the coronary thrombosis might be masked by dyspnea.

3. All cases of hemiplegia should have a careful search made for any clue leading toward old or recent coronary thrombosis in addition to routine electrocardiographic tracings.

4. In order to establish the true incidence of cerebral embolism or cerebral thrombosis as a sequel of coronary thrombosis, we must examine the heart at autopsy in all cases that clinically have a cerebral lesion. Also we must examine the brain in all cases with coronary thrombosis that had any neurologic manifestations.

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OBSERVATIONS ON THE THERAPEUTIC VALUE OF SULPHANILAMIDE IN BETA-HEMOLYTIC STREPTOCOCCUS PHARYNGITIS.

By J. Roswell Gallagher, M.D.,

SCHOOL PHYSICIAN, PHILLIPS ACADEMY, ANDOVER, MASS.

During the past few years several reports of clinical and experimental studies of the chemotherapeutic effect of para-amino-benzene sulphanilamide and certain of its derivatives in beta-hemolytic streptococcus infections have appeared in the foreign literature, and more recently Long and Bliss,[1a,b] and Marshall *et al.*[2] have made important contributions in this country. These studies have suggested that sulphanilamide may be of considerable benefit in the treatment of acute beta-hemolytic streptococcus infections, and convince one that these substances should receive further clinical trial. We have recently had the opportunity of evaluating its use in a series of 33 cases of beta-hemolytic streptococcus pharyngitis in a group of adolescents. In such a group this type of infection is important, not only because of its communicability but also because of the tendency for throat cultures to remain positive for a long period of time and consequently necessitate a long isolation period after apparent recovery from illness. Our interest in the use of sulphanilamide in these infections has been centered chiefly in determining whether or not its use might shorten the period during which throat cultures remain strongly positive. It is obvious that the throat culture is not an accurate quantitative method of determining the effect of any chemical on beta-hemolytic streptococci which have invaded the mucous membranes; but it is the only method applicable to this study and we feel that the frequency and care with which throat cultures were taken have somewhat reduced its unreliability. The rapidity of the absorption of sulphanilamide when given by mouth and its subsequent concentration in the blood and other body fluids has been investigated and it seems probable that it would inhibit the growth of bacteria in the mucous membrane of the pharynx.

Material. The 33 cases of beta-hemolytic streptococcus pharyngitis occurred in previously healthy young males ranging from 14 to 20 years. We have omitted data on a few other cases which either were not under

our care during their entire illness, or which developed some accompanying illness making their clinical course unsatisfactory for comparison.

In Table 1 are shown clinical data on the first 14 cases. Fever persisted from 2 to 7 days, 3 days being the most usual duration, and did not ordinarily exceed 102° F. There was leukocytosis in all cases ranging from 10,500 to 23,700 white blood cells per c.mm. At no time was there any evidence that the infection was milk-borne or carried by food handlers. In one column the initials of the individual who had contact with that patient before the onset of his illness are given; these data seem to indicate that the epidemic was definitely of the contact type. No definite history of exposure to other members of the group could be obtained from two individuals. Similar clinical data on the next 19 cases are given in Table 4; their clinical courses seemed essentially the same as those of the members of the first group.

TABLE 1.—CLINICAL DATA ON THE FIRST 14 CASES.

Name.	W.B.C. on adm. (thous.)	Days of fever.	Highest temperature.	Date admitted.	Contact.
A. W.	17.9	3	103.5	2–5	First case
D. J.	16.6	5	102	2–6	A. W.
J. F.	15.3	2	100	2–7	D. J.
J. E.	13.9	7	101.5	2–8	J. F.
F. C.	13.8	3	101.8	2–8	?
D. K.	10.5	2	101.8	2–8	D. J.
T. C.	18.4	3	101.6	2–9	F. C.
S. W.	23.7	3	101.5	2–10	D. K.
A. H.	20.3	2	101	2–11	F. C.
R. A.	18.2	3	102	2–12	A. H.
L. B.	14.6	2	101	2–14	A. H.
R. B.	13.9	4	101.5	2–15	L. B.
W. M.	15.5	2	102	2–15	?
B. J.	14.2	2	102.2	2–16	R. B.

Procedure. At the beginning of the outbreak it was felt desirable to withhold specific treatment from 10 individuals for about 10 days, so that we could determine whether the throat cultures would remain strongly positive for at least that length of time. The data in Table 2 show that 12 of the 14 patients had strongly positive throat cultures for more than 10 days. In the first group, 6 cases were given 40 grains of sulphanilamide daily (approximately 0.5 gm. per 10 kilos of body weight), in 4 equally divided doses beginning not earlier than the 11th day; 4 patients received 100 grains of sulphanilamide daily (approximately 1 gm. per 10 kilos of body weight), beginning not earlier than the 14th day; and 4 were given 40 grains daily beginning on the second or third day of illness. These 14 cases gave us an opportunity to determine about how long we might expect cultures to remain positive and an opportunity to develop some familiarity with the therapeutic agent.

Table 3 gives data on the next 19 cases. Eight of these patients were given daily doses of sulphanilamide equivalent to 1 gm. per 10 kilos of body weight, starting on from the 4th to the 6th day of the disease. The other 11 cases were given similar doses of sulphanilamide but therapy was begun not later than the 3d day of the disease. In addition to specific therapy each patient was given only such usual treatment as forced fluids, and frequent hot saline throat irrigations. Throat cultures were taken almost daily and were streaked on blood agar plates without delay.

A practically pure culture of beta-hemolytic streptococcus has been recorded as +++, a marked predominance ++ and the presence of a few colonies +.

TABLE 2.—DATA ON THROAT CULTURES AND SULPHANILAMIDE THERAPY FOR THE FIRST 14 CASES.

Name.	Day sulphanilamide started.	Number of days given.	Daily amount (grains).	Day of disease. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
A. W.	12	5	40	+++			+++			+++			++	++	+++	++	○	○	○					
D. J.	13	5	40	++	+++			++			+	++	++	○	+++	++	+	○	○		○			
J. F.	12	6	40	+++	+++			++	+++			++		++	++	+	○	+	○	○	○			
J. E.	12	8	40	+++	+++			++		++		+++		++	+++	+	+++	++	+	+	○	○	○	
F. C.	11	6	40	+++	+++			++	++			+++	++	++	○	○	+	○	○	○				
D. K.	10	5	40	+++		++		++		+	○	++	+	+	○	○	○							
B. J.	2	7	40	+++	+++	++	+	○	○	○	○													
W. M.	2	8*	40*	+++	○	+	+++	+++	+++	++	++	+	++	++*	○	++	+	+	+	○	○	○	○	
R. B.	3	9†	40†	+++	+++	++	+++	+++	+++	++	+++	+++	+++	+++	†		++	○	++	+++	++	++++	++	
L. B.	3	8‡	40‡	+++	+	+	+	++	++	○	○	++	++	+++	++	+++‡	++	○	○	○				
R. A.	14	4	100	+++						+++			++	○	○	++	+++	○	○	○				
J. H.	16	3	100	+++				+			○	++	○	+	○	++	○	+	+	○	○			
S. W.	16	3	100	+++				+		+++	++	++	++	++	+++	+++	+	+++	+	○	○	○		
T. C.	14	8	100	+++				++		○	+	○	+++	+++	+++	++	+++	++	++	○	++	○	○	○

* Sulphanilamide 100 gr. daily starting 11th day for 6 days.
† Sulphanilamide 100 gr. daily starting 12th day for 4 days; transferred for care elsewhere on 16th day. ‡ Sulphanilamide 100 gr. daily starting 13th day for 3 days.

TABLE 3.—DATA ON THROAT CULTURES AND SULPHANILAMIDE THERAPY FOR THE GROUP OF 19 CASES.

Name.	Day sulphanilamide started.	Number of days given.	Daily amount (grains).	Day of disease. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
G. I.	6–12*	33*	100	+++	+++	+++	+++	+++	+++	++	○	○	++	+++	++	○	+++	○	+++	+++	++	○	○	○
P. B.	4	3	100	+++	+++	++	+++	○	○	○	○													
J. O'B.	6	5	100	++	○	++	+++	+++		++	++	++	+++	++	++	++	+	++	++	○	○	○	○	
J. G.	5	5	100	+++	+		+++		+	○	+	+	+++	+++	○	○	○	○						
R. O.	5	4	120	+++	+++	+++	+++	+++	++	++	○	○	○	○										
J. W.	5	5	100	+++	+++	+++	+		++	+	○	+	++	+	+	○	○	○						
O. B.	4	4	90	+++	+	+++	+++	++	○	○	○													
S. D.	5	5	75	+++	+++	++	+++	+++	++	○	○	○												
S. B.	2	10	90	+++	+++	++	+++	+++	○	+++	+++	+++	○	○	○	○								
D. P.	2	10	100	+++	+++	++	+++	++	+++	+	++	○	○	○	○									
G. P.	2	6	90	+++	+++	+++	++	+++	+++	++	+++	+++	++	+	+++	+++		+++		+++		+++	+++	+++†
J. McL.	2	5	90	++	+++	+++	++	○	○	○	○													
C. H.	3	5	120	++	++	+++	++	+++	○	+	+++	+	○	○	○									
W. D.	3	5	90	+++	+++	+++	++	○	○	○	○													
W. S.	2	5	100	+++	+++	+	++	++	++	++	+++	○	+++	+++	++	++	○	++	○	○	○			
J. L.	1	4	100	+++	+++	○	○	○																
H. P.	2	4	90	+++	+++	○	○	○	○															
J. A.	2	5	90	+++	+++	+++	+++	+++	++	+++	+++	+++	+++	++	+++	+	○	○	○					
T. B.	2	4	100	+++	+++	+++	+	○	○	○	○													

* Interval of 3 days without sulphanilamide. † To 25th day + + +, then transferred elsewhere for further care.

The streptococci were isolated in pure culture from 12 patients. These 12 strains were then incubated at 37° C for 17 hours in blood broth, 0.1 cc. of this growth was added to 5 cc. of blood broth, and after 7 hours incubation dilutions of 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} were made in nutrient broth. One cc. of these dilutions was inoculated intraperitoneally in mice, and at death cultures were made from heart's blood and peritoneal exudate. No mice died within 7 days when the dilution was greater than 10^{-1}.

Results. In the first group of 14 patients, members of which were given only small doses of sulphanilamide or larger doses very late in the disease, the throat cultures remained positive for 12 days or more in 13 patients and for 16 days or more in 6 patients; 5 of the 6 patients who were given small doses of sulphanilamide late in their disease showed negative throat cultures almost directly, but it seems unlikely that the treatment was responsible for this result. It seems more probable that these throat cultures would have become negative at that time if no treatment had been given. Similar results followed the use of larger doses of sulphanilamide late in the illness of 4 patients; but it is difficult to believe that the drug could have effected a change so rapidly. Four patients received small daily doses of sulphanilamide starting early in their disease, and in only one instance was the period of positive throat cultures definitely shortened. The data obtained in this group indicate the length of time during which throat cultures tend to remain positive for beta-hemolytic streptococcus in this type of illness and is important for comparison with the second group of patients. Data in Table 3 indicate that different results were obtained when larger doses of sulphanilamide were given early in the disease (clinical data concerning this group are given in Table 4). In this group of 19 patients only 6 patients had a positive throat culture on the 12th day, in contrast with 13 out of 14 patients in the other group. Only 3 of the 19 had positive cultures on the 16th day, in contrast to 6 patients out of 14 patients in the other group. In the first group only 1 patient out of 14 had a negative throat culture on the 5th day of his illness, while in this group 6 out of 19 patients had negative cultures on that day. The number of patients in the two sections of this group, *i. e.*, those who were given sulphanilamide on or before the 3d day and those who started treatment from the 4th to the 6th day, is too small to permit one to draw definite conclusions; but it does not appear that this degree of delay in starting therapy affected the results; however, there does not seem to be any advantage in delaying the therapy. In this group of 19 patients there were 5 who seemed to have received little or no benefit from the sulphanilamide; there was nothing in their past histories nor any peculiarity in their upper respiratory tracts nor in the course of their illnesses which was noticeably different from that of other members of the group. It seems much more likely that these individuals were infected with a strain which is not affected by sulphanilamide; but it is possible that these

patients either absorbed the drug very poorly or excreted it very rapidly. There can be little doubt in the mind of anyone who has worked with even such a small group of patients as this that, in a significant proportion of individuals who have been infected with certain strains of beta-hemolytic streptococcus, sulphanilamide will inhibit the growth of the bacteria. The strains isolated from these patients were of low virulence for mice as were those strains isolated from several other patients.

TABLE 4.—CLINICAL DATA ON THE GROUP OF 19 CASES SIMILAR TO THAT GIVEN IN TABLE 1 FOR THE FIRST 14 CASES, AND IN ADDITION DATA ON THE TOXIC SYMPTOMS WHICH DEVELOPED.

Name.	Days fever.	Highest temperature.	W.B.C. on adm. (thous.)	Day sulphanilamide started.	Day headache.	Day rash.	Day cyanosis.	Day abdo. cramps.
G. I.	3	100	11.0	6	7	..	15	
P. B.	3	100	13.0	4	6	..	..	6
J. O.	2	100.8	19.6	6				
J. G.	2	100.2	14.6	5	..	13		
R. O.	2	101.8	16.2	5	7	..	8	
J. W.	1	100	17.7	5	..	12	8	
O. B.	2	99.6	14.7	4				
S. D.	3	102	18.2	5	7			
S. B.	2	102	16.2	2	3			4
D. P.	3	102	12.9	2	3	12	11	
G. P.	2	101.5	19.8	2	3	11	10	
J. M.	2	100.5	13.8	2	3			
C. H.	2	99.8	10.0	3	..	10	..	9
W. D.	2	102.8	12.8	3				
W. S.	2	102	11.7	2	..	..	5	
J. L.	2	100	15.7	1				
H. P.	2	101.8	14.8	2	..	..	4	
J. A.	3	102.8	14.6	2	7	..	5	
T. B.	2	102.5	14.6	2	..	..	5	

Toxic Effects. In the course of this study we have observed certain toxic effects of sulphanilamide (Table 4). No toxic effects were observed in the patients who received only 40 grains of sulphanilamide daily; 2 patients in the first group who received 100 grains became slightly cyanosed, but there were no other significant manifestations of toxicity in that group. Of the 19 patients who received about 1 gm. per 10 kilos of body weight daily, 9 developed headache accompanied by slight elevation in temperature on from the 2d to the 4th day after therapy was begun; and 9 became moderately cyanosed from the 4th to the 10th day of treatment. The precaution of not using saline laxatives has been advised and none of these patients received such medication. Three individuals complained of abdominal cramplike pain, which may have been caused by the sulphanilamide. Five patients developed a morbilliform type of rash which was widely distributed over the arms, neck and chest; this rash appeared on from the 10th to the 13th day after the therapy was begun, caused little discomfort, and disappeared within 3 or 4 days.

Summary. 1. Observations on the value of sulphanilamide in 33 cases of pharyngitis caused by strains of beta-hemolytic streptococcus of low virulence for mice are reported.

2. The administration of doses of sulphanilamide in amounts equivalent to 1 gm. of sulphanilamide per 10 kilos of body weight daily early in the course of these cases of beta-hemolytic streptococcus pharyngitis apparently shortened the length of time during which throat cultures continued to be positive for those bacteria in a significant proportion of cases.

3. The results obtained in this study suggest that small doses of sulphanilamide given early in such an illness are usually without demonstrable effect. When small or large doses are given late in such an illness, it is impossible to be certain that subsequent throat cultures have become negative because of the specific therapy.

4. The use of sulphanilamide in adequate dosage frequently produced mild toxic symptoms, such as headache, cyanosis and a morbilliform dermatitis; none of these manifestations were followed by serious consequences.

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THE INACTIVATION OF ESTROGEN BY THE LIVER.

OBSERVATIONS ON THE FATE OF ESTROGEN IN HEART–LUNG AND HEART–LUNG–LIVER PERFUSION SYSTEMS.*

BY S. LEON ISRAEL, A.B., M.D.,

INSTRUCTOR IN GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA; ADJUNCT GYNECOLOGIST, MOUNT SINAI HOSPITAL,

DAVID R. MERANZE, B.S. (CHEM.), M.D.,

DIRECTOR OF LABORATORIES AND PATHOLOGIST, MOUNT SINAI HOSPITAL, PHILADELPHIA, PENNA.,

AND

CHARLES G. JOHNSTON, M.S., M.D., F.A.C.S.,

PROFESSOR OF SURGERY, WAYNE UNIVERSITY COLLEGE OF MEDICINE, DETROIT, MICH.

(From the Department of Gynecology and the Laboratories of the Mount Sinai Hospital, and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania.)

DESPITE the rapid progress, during the last decade, in the isolation, purification, and synthesis of the estrogens, their clinical dosimetry remains largely empiric. This is frequently the case with newly introduced therapeutic agents of low toxicity. However, when the clinical effects of a new agent are better understood, interest then centers upon a more exact administration of the sub-

* This work was aided by a grant from the Samuel S. Fels Fund for Medical Research.

stance. This must in fact depend on a knowledge of the rate of utilization and the disposal level of the substance when administered in known quantities. The renal threshold for estrogen has been a subject of considerable study ever since Loewe and Lange[1] demonstrated its presence in the urine of normal women. Through the work of many investigators[2] we now know the urinary and fecal levels of estrogenic substance in health and disease. However, it has been apparent that the rate of disappearance of estrogens in the body varied under different physiologic and pathologic circumstances, and a knowledge of these variations has become essential for evaluation of the proper dosage.

Recently, many studies have been carried out in both animals and man in the hope of determining the fate of estrogens in the body under normal and abnormal conditions. These experiments have shown that most of the estrogen administered is not excreted, at least, not in a form recognizable by our present-day methods of detection. The total quantity of estrogen excreted, following oral or hypodermic administration to amenorrheic,[3] pregnant,[4] menopausal,[5,6] or castrated[7] women, and to males,[4] has been shown to be no more than 20% of the amount administered. The actual amounts recovered varied from 3 to 20%, depending upon whether the fecal and urinary excretion was determined, and whether a hydrolysation technique of extraction[8] was used. It was also observed[3,4,5,7] that the maximum excretion of the estrogenic substance occurred within the first 24 hours of its administration, and that the excretion ceased after from 48[4,5] to 96 hours,[7] irrespective of the quantity administered. These observations on the speed with which administered estrogen is excreted are in agreement with the experimental data of McClendon, Burr and Conklin.[9] Thus, while all observers agree that only a small portion of administered estrogen is eliminated as such from the body, there is no unanimity of opinion concerning the fate of the remainder.

Several investigators have attempted to determine the nature and site of the destruction of the estrogens, and the speed with which this occurs. Frank, Goldberger and Spielman[10] have shown that estrogen, administered intravenously or subcutaneously in doses of from 2000 to 3000 mouse units to isolated female rabbits, disappears from the blood after 30 minutes and is not recovered from any of the organs extracted 24 hours after injection, except for small traces in the liver. A similar experiment in monkeys showed that only 20% of administered estrogen was excreted by the kidneys. These investigators concluded that the remainder of the estrogen was not stored in the body, but was either rapidly destroyed, or altered. Silberstein, Molnar and Engel,[11] working with the blood and liver of healthy male dogs, showed that both tissues, either together or separately, destroyed estrogen *in vitro*. They also demonstrated the degree and speed of estrogen destruction in

incubated dog blood to be 50% in 10 minutes, 80% in 30 minutes, and 96% in 120 minutes. The ability of liver tissue to destroy estrogen *in vitro* has been observed by others, but the efficacy of blood in this regard has not been corroborated. Fee, Marrian and Parkes,[12] employing the isolated heart-lung-kidney preparation of Starling and Verney,[13] showed that only 1% of the total amount of estrogen introduced into the artificial circulatory system was excreted by the kidney. They also noted that the estrogen disappeared from the circulating blood of the artificial system within 25 minutes, only traces remaining in the heart, lungs and kidneys at the conclusion of the experiment. Their control mixtures of blood and estrogen, incubated at either 37° C. or at room temperature for 3 hours, showed no loss of estrogenic activity. Observing that estrogen rapidly disappeared from a heart-lung-kidney perfusion system and yet was not excreted by the kidney, destroyed by the blood, or stored in the organs, Fee, Marrian and Parkes postulated that the loss may be effected by an oxidation process in the pulmonary circulation.

Zondek,[14] having found that rodents excrete none and humans only 3% of administered estrogen, attempted to discover the fate of the "retained" estrogen by extracting and assaying the finely-ground bodies of rodents at from 3 to 72 hours after the injection of estrogen. He recovered less than 1% of the injected estrogen by ordinary, neutral, extraction, but recovered larger amounts by an hydrolysation, acid-boiling, technique. Employing the latter method, Zondek recovered 20% of the estrogen after 24 hours, 6% at 48 hours and 1% at 72 hours. Concluding that estrogen administered to rats is neither stored nor excreted, and that it is either chemically altered or completely destroyed, Zondek sought the site of the change by determining the loss of estrogenic potency occurring in incubated mixtures of estrogen and various rodent organs. Of all the organs, only the liver showed a consistent effect on the added estrogen. In 5 of 7 experiments, the liver-estrogen mixtures showed more than 90% loss of estrogenic potency in 5 hours, whether or not acid hydrolysis was performed. More interesting are Zondek's further observations that, although aqueous and dried liver extracts would inactivate estrogen, boiled liver would not do so. On the basis of these *in vitro* experiments, Zondek postulated the existence of an hepatic enzyme, "œstrinase," capable of inactivating estrogens. Further indication that the liver may have a rôle in the metabolism of estrogens is found in the recent work of Rondoni, Carminati and Corbellini,[15] who described the formation of an estrogenic substance by the interaction of cholesterol and liver tissue *in vitro*.

Although the experimental data cited indicate that the major portion of administered estrogen is altered in the body and further suggest that the liver effects the change, there is no unanimity of opinion concerning either the nature or the site of the process.

Our experiments were planned in an attempt to resolve the contradictory evidence[11,12,14] concerning the effect of mammalian blood on estrogenic potency and to evaluate the possible existence of an hepatic "œstrinase."[14] Believing that *in vitro* experiments which employ isolated tissues and invite a rich bacterial invasion are open to criticism, we sought a more physiologic experimental technique. Thus, in order to determine the effects of blood,[11,12,14] lungs,[12] and liver[14] on estrogen under similar conditions, perfusion experiments were chosen. It was thought that studies showing the comparative rates of disappearance of estrogen from mammalian blood *in vitro* and from mammalian blood circulating in heart-lung and heart-lung-liver preparations would be of crucial import. Perfusion experiments of the isolated liver[16] are not entirely satisfactory. We therefore used the heart-lung preparation of Knowlton and Starling[17] as a perfusing motor. Such heart-lung-liver preparations have been previously employed in studies of the detoxification of strychnine,[18] quinidin[19] and ouabain.[20] This technique, properly executed, affords adequate perfusion and maintains the functioning state of the liver, as is evidenced by the previous reports,[18,19,20] and by our own observations which included histologic study of the perfused liver at the conclusion of the experiment (Figs. 1 and 2).

Perfusion Experiments. The apparatus used in the perfusion experiments was essentially the same as that employed by previous workers.[18,19,20]

Two types of experiment were done. In the first series, the fate of a known amount of estrogen* introduced into heart-lung preparations was studied; and in the second series, the same objective was sought in heart-lung-liver preparations. This was accomplished by introducing into the circulation of a stabilized perfusion system known amounts of estrogen and withdrawing blood samples for estrogen-assay at intervals. Each experiment continued for at least 1 hour, a minimum of 4 blood samples being obtained. At the end of each experiment, the heart, lungs and liver were separately assayed for estrogen after alcohol extraction in a Soxhlet apparatus for 24 hours.

The experiments were performed in an identical manner. The dogs employed were anesthetized by sodium amytal (50 mg. per kilogram of body weight). In each experiment, the control specimens for estrogen-assay consisted of: 1, 30 cc. of perfusion blood removed from the system prior to the addition of estrogen (blood control); 2, a similar quantity of perfusion blood to which a known amount of

* The estrogen employed throughout these experiments was crystalline alpha-ketohydroxyestrin ($C_{18}H_{22}O_3$). One milligram of this crystalline substance is equivalent to 900 rat units in bio-assay. Prior to each experiment, 2 milligrams of the crystals (1800 rat units) were dissolved in 180 cc. of phosphate buffer (pH 7.9), bio-assayed, and employed as the stock solution for that one experiment. (The estrogen was supplied through the courtesy of Dr. Erwin Schwenk of the Schering Corporation.)

estrogen was added (blood-estrogen control); and, 3, a sample of the estrogen solution employed. The control specimens and the samples of blood withdrawn during the experiments were dried with anhydrous sodium sulphate, extracted for estrogen by the method of Frank and Goldberger[21] and assayed on castrated adult rats (Allen and Doisy[22]). The test rats employed in the assays weighed from 140 to 160 gm. Following castration, vaginal smears were examined daily for a minimum of 2 weeks to insure the presence of continuous anestrus. Each rat was then tested for sensitivity, and only those animals showing vaginal estrus in response to 1 rat unit of estrogen were used. From 16 to 30 rats were used in each assay. In the actual experiments we considered a positive reading to be the presence of estrus (vaginal smear technique) in both of the two rats employed in the final reading of each assay. The rats employed in those assays which yielded zero readings (less than 2 rat units) were retested for sensitivity with standard estrogen to insure the validity of these findings.

A protocol, typical of each perfusion experiment, is presented below.

TABLE 1.—DATA OF A HEART-LUNG PERFUSION EXPERIMENT, SHOWING THE NON-INACTIVATION OF ESTROGEN.*

Blood specimen number.	Minutes after introduction of estrogen.*	Estrogen content of 30 cc. blood specimen in rat units.
1	15	15
2	30	30
3	45	20
4	60	15

CONTROL AND TISSUE ASSAYS.

	Estrogen content in rat units.
Blood Control: 30 cc. of perfusion fluid removed prior to introduction of estrogen	less than 2
Blood-estrogen Control: 30 cc. of perfusion fluid plus 30 rat units of estrogen	30
Heart (at conclusion of experiment)	96
Lungs (at conclusion of experiment)	72

* 1000 rat units of estrogen added to approximately 1270 cc. of circulating perfusion fluid.

Protocols. *Heart-lung Perfusion* (*Table 1*). A heart-lung preparation was established in a dog weighing 8.6 kilograms, from which 200 cc. of blood had been previously taken. This blood and an additional 770 cc. of blood obtained from two other dogs were defibrinated, heparinized and introduced into the circuit of the preparation. A small amount of heparin was added to the blood circulating in the perfusion system to safeguard further against coagulation. The pressure of the circulatory system was appropriately regulated throughout the experiment. The perfusion circulation being well stabilized, 60 cc. of blood were removed at 12.15 P.M. Of this amount, 30 cc. were incubated at 37° C. for the duration of the experiment and then titrated for estrogen (blood control, Table 1). The remaining 30 cc., to which were added 30 rat units of estrogen in buffered solution, were likewise incubated and subsequently assayed (blood-estrogen control, Table 1). Immediately following the obtaining of the blood (60 cc.) for control analysis

at 12.20 P.M., 1000 rat units of estrogen in 100 cc. of buffered solution were introduced into the perfusion system. During the next hour 30 cc. specimens of blood were removed for bio-assay at each 15-minute interval. At the termination of the experiment, the heart-lung preparation was actively functioning. The heart and lungs were removed, extracted and assayed for estrogen.

TABLE 2.—DATA OF A HEART-LUNG-LIVER PERFUSION EXPERIMENT, SHOWING THE INACTIVATION OF ESTROGEN.*

Blood specimen number.	Minutes after introduction of estrogen.*	Estrogen content of 30 cc. blood specimen in rat units.
1	15	Less than 2
2	30	Less than 2
3	45	Less than 2
4	60	Less than 2
5	75	Less than 2
6	105	Less than 2

CONTROL AND TISSUE ASSAYS.

	Estrogen content in rat units.
Blood Control: 30 cc. of perfusion fluid removed prior to introduction of estrogen	Less than 2
Blood-estrogen Control: 30 cc. of perfusion fluid plus 30 rat units of estrogen	30
Heart (at conclusion of experiment)	4
Lungs (at conclusion of experiment)	40
Liver (at conclusion of experiment)	20

* 1000 rat units of estrogen added to approximately 870 cc. of circulating perfusion fluid.

Heart-lung-liver Perfusion (*Table 2*). A heart-lung circuit was established in a dog weighing 6 kg. and 670 cc. of blood obtained from two other dogs were defibrinated, heparinized and added to the system's reservoir. At 10.25 A.M., in less than 3 minutes of its excision, the liver of a healthy dog weighing 10.5 kg. was joined to the heart-lung circuit by the usual technique. At 10.40 A.M., the control 60 cc. of blood were removed from the circulation. Of these 60 cc., 30 cc. were incubated at 37° C. for the duration of the experiment and then titrated for estrogen (blood control, Table 2). The remaining 30 cc., to which were added 30 rat units of estrogen in buffered solution, were likewise incubated and subsequently assayed (blood-estrogen control, Table 2). Immediately after withdrawal of the controls, at 10.45 A.M., 1000 rat units of estrogen in 100 cc. of buffered solution were introduced into the perfusion circulation. Thereafter, at 15-minute intervals from 11 A.M. to noon, and 12.30 P.M.—30 cc. specimens of blood were removed for estrogen titration. Adequate heart action and liver circulation were maintained throughout the experiment. At the end of the experiment, the heart, lungs and liver were removed, separately extracted and assayed for estrogen.

Discussion. Strikingly uniform results were obtained in each series of experiments. It was shown that no destruction of estrogen occurs in canine blood *in vitro* (blood estrogen controls, Tables 1 and 2). These observations are not in agreement with those of Silberstein,[11] but are in agreement with those of other workers.[12,14] Similarly, the estrogen concentration remained unaltered in the heart-lung perfusion experiments. The amount of estrogen in the

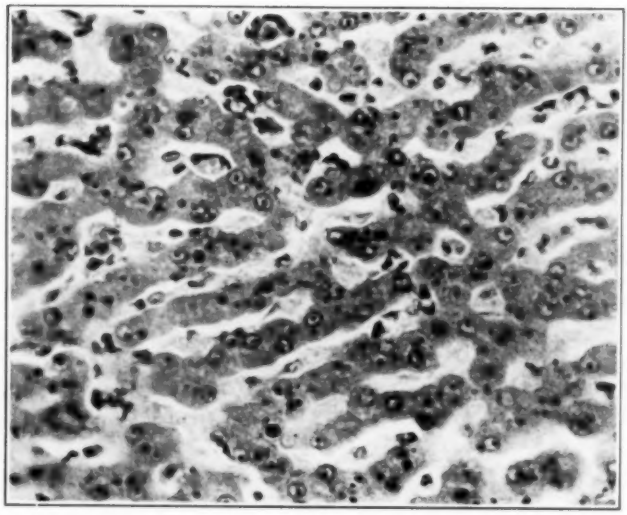

FIG. 1.—Photomicrograph of dog liver at the conclusion of heart-lung-liver perfusion experiment, showing slight cloudy swelling. (× 500.)

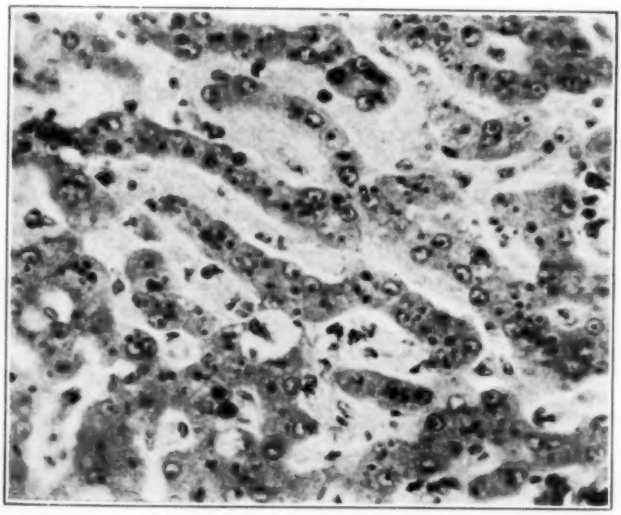

FIG. 2.—Photomicrograph of dog liver at the conclusion of heart-lung-liver perfusion experiment, showing moderate cloudy swelling and dilated sinusoids. (× 500.)

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30 cc. samples of blood, removed every 15 minutes throughout each of the heart-lung experiments, remained essentially the same (Experiments I and II, Table 3). It may be objected, in regard to the heart-lung perfusion experiments, that a partial loss of estrogen occurred within the first 15 minutes and that the amounts of estrogen recovered subsequently represented equilibrium conditions. We do not believe that this objection is a valid one. Estimating the total amount of fluid which circulated in one of the heart-lung experiments to be 1270 cc. (200 cc. remaining in the dog's heart-lung circuit, 970 cc. of defibrinated blood added to the system, and 100 cc. of estrogen solution containing 1000 rat units), the control concentration of estrogen approximated 0.8 rat units per cc. This concentration of estrogen remained practically stationary throughout the experiment (Experiment I, Table 3), indicating that no loss of estrogen occurred. This does not imply that the amount of circulating fluid remained constant throughout the experiment. Actually, a certain loss of fluid-volume inevitably occurs in all perfusion experiments because of unavoidable leakage. This is illustrated by the data of the same heart-lung experiment (Experiment I, Table 3), wherein the initial level of circulating fluid was 1270 cc. and the final level, as measured by air-irrigation and drainage of the system, equalled 850 cc. There is no reason to suppose, however, more especially since the estrogen is added in a perfectly admixed aqueous solution, that the lost blood is selectively deprived of its estrogen content as it leaks from the circuit. Our findings are not in accord with those of Fee, Marrian, and Parkes,[12] who postulated that estrogen is lost by pulmonary oxidation in a heart-lung perfusion system. The data of our heart-lung perfusion experiments force us to conclude that no loss of estrogen occurs in such a system.

TABLE 3.—DATA OF HEART-LUNG AND HEART-LUNG-LIVER PERFUSION EXPERIMENTS, SHOWING THE FATE OF ESTROGEN.*

Blood specimen (30 cc.).	Estrogen content in rat units.				
	Heart-lung.		Heart-lung-liver.		
	Exper. I.	Exper. II.	Exper. III.	Exper. IV.	Exper. V.
15 min.	15	15	Less than 2	Less than 2	10
30 min.	30	30	Less than 2	Less than 2	5
45 min.	20	30	Less than 2	Less than 2	Less than 2
60 min.	15	30	Less than 2	Less than 2	Less than 2
75 min.			Less than 2	Less than 2	Less than 2
105 min.			Less than 2	Less than 2	Less than 2
Organs at end of experiment.					
Heart	96	90	4		10
Lungs	72	90	40	30	99
Liver			20	45	60

* 1000 rat units of estrogen added to perfusion fluids which varied from 870 cc. to 1270 cc. in volume.

The results of the heart-lung-liver perfusion experiments are in striking contrast to the above-described observations (Table 3). Estrogen was rapidly and completely removed from the circulation in each of the 3 heart-lung-liver perfusion experiments. With a single exception this removal was complete within 15 minutes. This disappearance of estrogen represents, we believe, an actual inactivation of the substance, and may be seen from the final analyses of the organs perfused (heart, lungs and liver). It is noteworthy that the amounts of estrogen found in the heart and lungs of the heart-lung-liver perfusion experiments were, with a single exception, less than those found in the corresponding organs of the heart-lung experiments. This is further evidence that the final concentrations of estrogen circulating in the heart-lung-liver systems were definitely lower than those in the heart-lung circuits. Of even greater interest was the low content of estrogen in the liver, an organ weighing more than the combined weights of the corresponding heart and lungs. These data, corroborative of Zondek's[14] *in vitro* experiments, suggest but in no wise prove the existence of an hepatic "œstrinase." The recent work of Cohen and Marrian,[23] showing that estrogenic substance is found in the urine of pregnant women in the form of a glucuronate ("œstriol glucuronic acid"), is of interest. Inasmuch as glucuronic acid is synthesized in the liver, the findings of Cohen and Marrian strengthen the link between the liver and the process of estrogen alteration. Whatever the mechanism by which the change is effected, it does appear that the liver in some manner inactivates estrogen.

That the liver of such a perfusion circuit is capable of performing many of its ordinary functions has been demonstrated by previous workers.[18,19,20] The liver retained its normal color throughout each experiment. Gross evidence of edema did not appear. The hepatic blood flow remained continuous, and no areas of rupture or intrahepatic hemorrhage were noted. The blood entering the liver was red and that leaving it was such as to suggest that in its passage through the liver, oxygen utilization by the liver cells occurred. The photomicrographs of portions of two livers, prepared at the end of 2 experiments, show only the congestion and cloudy swelling anticipated from the conditions of the perfusion system (Figs. 1 and 2).

It is not surprising that so much estrogen is removed from the circulation of a heart-lung-liver preparation within the short time of 15 minutes. In the *in vivo* experiments of Frank, Goldberger and Spielman[10] estrogen was not found in the circulation after 30 minutes. Priestley, Markowitz and Mann[18] demonstrated, in heart-lung-liver perfusion experiments with strychnine, a concentration of the substance in the liver seven times greater than that in the circulating blood within 10 minutes. Similarly, a 50% decrease in concentra-

tion of circulating quinidin occurred within 13 minutes.[19] Though the conditions are not precisely parallel, it may be noted that the dyes (bromsulphalein, etc.) employed in certain liver function tests disappear normally from the circulating blood within 30 minutes.

Summary. 1. A review of the current concepts of the fate of estrogen administered to animals and human beings is presented. It appears that only from 3 to 20% of administered estrogen is excreted, the remainder being irrecoverable in analyses of body organs.

2. In an attempt to resolve the controversial views concerning the fate of the "lost" 80% of administered estrogen and to evaluate the rôle of the liver in this process, the comparative rates of disappearance of known amounts of estrogen from standing dog blood and from dog blood circulating in heart-lung and heart-lung-liver perfusion preparations were determined.

3. These experiments show that estrogen is not inactivated by dog blood *in vitro* or by the circulation in a heart-lung perfusion system. It is rapidly inactivated by circulation in a heart-lung-liver perfusion system.

4. From these observations, it is concluded that the liver, in some manner, either destroys or alters circulating estrogen.

The authors wish to acknowledge the constant aid and encouragement afforded them throughout the performance of the experiments by Drs. Isidor S. Ravdin and Maurice H. Friedman.

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HEREDITARY HYPOPLASIA OF THE MESENCHYME.

(Blue Sclerotics and Brittle Bones.)

By George E. Burch, M.D.,

INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; ASSISTING VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA,

AND

William A. Sodeman, M.D.,

INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA, NEW ORLEANS, LA.

(From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and from the Charity Hospital of Louisiana.)

In a 14-year-old white boy under treatment for acute hemorrhagic nephritis, blue scleræ were noted on physical examination. Further study showed that he had a fracture of the humerus 5 years previously. Roentgen ray examination revealed a moderate degree of arthrokatadysis (Otto's pelvis). A search of the family history disclosed the presence of blue scleræ in the brother and mother. A more careful analysis of the family tree led to the discovery of a group of individuals with hereditary hypoplasia of the mesenchyme, which group is larger than any we have been able to find in the literature. Because of the rarity of the condition and size of the family tree, we believe a brief report of our findings is warranted.

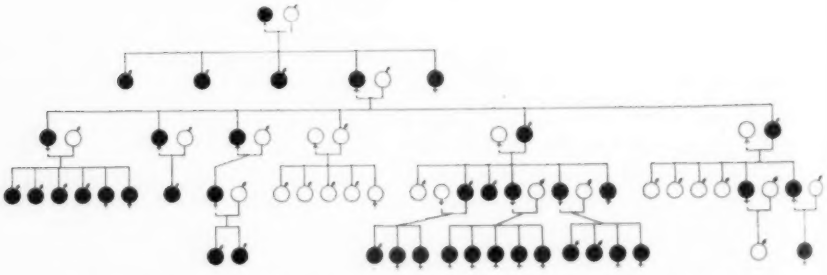

Chart I.—Family tree showing affected (black) and normal (white) individuals. Twenty-three normal members of the fifth generation, children of normal individuals of the fourth generation, are not shown.

Of 76 known individuals in the family, 53 are shown in the accompanying figure. The 23 individuals not illustrated were normal offspring of normal members shown in the fourth generation. These 23 individuals were omitted from the illustrated family tree because of insufficient sex data. Of the 76 people studied, 41 (53.9%) were found to be affected. Five affected members of the fourth generation, shown in the figure on the left, had many affected children.

Our information regarding the children is meager because of their inaccessibility, so that they could not be included in this presentation.

Every affected individual had an affected parent. The disease was transmitted 10 times by females and 3 times by males. Of the 41 affected individuals, 17 were males and 24 were females. This is in keeping with previous reports.[1,2] All of those affected had blue scleræ; 17 of them are known to have had one or more fractures. Our patient and his mother, grandmother and great-grandmother had varying degrees of deafness. The relative frequency of deafness for the entire group is unknown. Three of the affected individuals were small in stature with large skulls and prominent bossæ. This, however, was not true throughout the family tree. There was no evidence of hypermobility of joints as far as could be determined.

Comment. Idiopathic bone fragility is classified as follows:[1]

I. *Hereditary type:* 1. Hereditary hypoplasia of the mesenchyme (Brittle bones and blue scleræ).

II. *Non-hereditary congenital type:* 1. Osteogenesis imperfecta congenita. 2. Osteogenesis imperfecta tarda (osteopsathyrosis): *a*, With white scleræ; *b*, with blue scleræ.

III. *Non-hereditary acquired type:* 1. Osteosclerosis fragilis generalisata (Marble bones, or Albers-Schönberg's disease).

IV. *Senile type:* 1. Osteoporosis.

Our group is an example of the hereditary type. The heredity of the disease behaves according to the Mendelian law for a single dominant factor which is not sex-linked. The clinical picture is characterized chiefly by: 1, blue scleræ; 2, fragility of bones; 3, deafness, and 4, hypermobility and relaxation of joints. All affected persons have blue scleræ, but the other characteristics are variable. This proved to be true in our group. The blueness of the sclera is ascribed to hypoplasia of the sclerotic mesenchyme with a resulting thinness of the sclerotic coat which permits the choroid pigmentation to shine through. Similarly the hypoplasia of the mesenchyme explains the ease of fracture of the bones and the relaxation of the ligaments. While the affected individuals are usually described as small in stature, this was not true in many of the members of our group.

Summary. Of 76 known individuals in five generations of the family studied, 41 (53.9%) were affected with hereditary hypoplasia of the mesenchyme. This is a larger group than any we have been able to find in the literature.

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INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; ASSISTING VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA,

AND

WILLIAM A. SODEMAN, M.D.,

INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA, NEW ORLEANS, LA.

(From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and from the Charity Hospital of Louisiana.)

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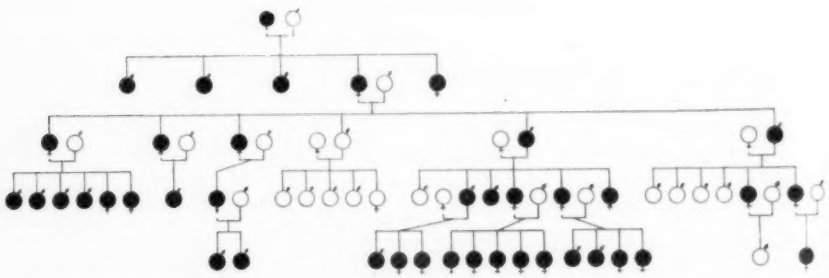

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THE TISSUE PRESSURE IN SUBCUTANEOUS EDEMA.

By William A. Sodeman, M.D.,
INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA,
AND
George E. Burch, M.D.,
INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA; ASSISTING VISITING PHYSICIAN, CHARITY HOSPITAL OF LOUISIANA, NEW ORLEANS, LA.

(From the Department of Medicine, School of Medicine, Tulane University of Louisiana and the Charity Hospital of Louisiana.)

In the mechanisms concerned in the control of fluid exchange across the small blood-vessel walls, the interplay of the osmotic pressure and hydrostatic pressure of the blood has been accepted as the major controlling force. The influence of comparable forces in the tissue outside of the blood-vessels has been largely neglected. The colloid osmotic pressure of the interstitial tissue fluids has been studied satisfactorily only in patients with edema where fluid sufficient for analysis has been collected. The amounts of interstitial fluid in the normal individual are so small that accurate analyses have been impossible. Tissue pressure, which is related to hydrostatic pressure within the blood-vessels, has only recently been directly determined in this country.[1a,b] It is with the influence of the latter factor, tissue pressure, that the present report is concerned.

Methods and Materials.—The method used in these determinations is that previously described.[1b] It consists essentially of a U-tube water manometer connected by rubber tubing to a rubber pressure bulb controlled by a screw clamp and also connected to a glass adapter to which is fastened a 26-gauge needle. The opening in the bevelled end of the needle was occluded with solder and 4 openings symmetrically drilled into the lumen through the wall of its distal third. In use, sterile normal saline was drawn into the needle and about half way up the adapter and the pressure in the system was then brought to atmospheric. The needle was then inserted into the subcutaneous tissues of the part to be studied and the pressure within the system was slowly raised by the screw clamp until the meniscus in the adapter just began to move. This pressure was taken as the subcutaneous tissue pressure. All determinations were made under aseptic technique. Three readings were taken which agreed within ± 1 mm. of water for each determination. The part rested passively without movement or constriction throughout the determination.

Determinations were made on 23 subjects with various types of edema. Only subjects with increasing edema were chosen. With 2 exceptions all determinations were made in the pretibial area in patients confined to bed. In the patients with histamine edema

(0.5 cc. of 1 to 1000 histamine phosphate subcutaneously) and with scleroderma, the determinations were made in the arm. The causes of the edema were as follows: congestive heart failure, 10; acute hemorrhagic nephritis, 3; low serum proteins, 2; beriberi, 2; operative trauma, 2; pernicious anemia, 1; toxemia of pregnancy, 1; erysipelas, 1; histamine, 1. The edema of operative trauma developed in 1 patient with marked scleroderma following a stellate ganglionectomy, and in another patient following the removal of a tumor about the ankle.

TABLE 1.—SUBCUTANEOUS TISSUE PRESSURE DETERMINATIONS IN VARIOUS TYPES OF EDEMA.

Subject No.	Cause of edema.	Day of observation.															
		1	2	3	4	5	7	8	9	10	11	12	13	14	16	20	21
1	Cong. heart fail.	181	188	148	Died												
2	Cong. heart fail.	126	122	42	32	60	58										
3	Cong. heart fail.	60	Died														
4	Cong. heart fail.	208	242		194			180	Died								
5	Cong. heart fail.	116	52		52	98		69			58		70		64	49	
6	Cong. heart fail.	156	140			142		106	100	Died							
7	Cong. heart fail.	110		40	38	40											
8	Cong. heart fail.	218			262		218										*86*
9	Cong. heart fail.	70		50		50	52			44				*56*			
10	Cong. heart fail.	47	58														
11	Beriberi	124	68						50								*58*
12	Beriberi	86						42									
13	Nephritic	102			*51*												
14	Nephritic	106															
15	Nephritic	94															
16	Nephrotic	78				150		Died									
17	Nephrotic	62		61													
18	Scleroderma	*280*	*				338										216
19	Per. anemia	114			158	122										150	
20	Tox. preg.	88	161				102					*46*					
21	Post. op.	41						*26*									
22	Erysipelas	188															
23	Histamine	246															

* Cervical sympathectomy performed.
Italicized numbers indicate that the patient was edema-free.

Results. (Table 1.) The extremes of the values in the patients with cardiac edema and the course of the tissue pressure in 5 of them were previously reported.[15] In all the subjects studied with increasing edema, regardless of the cause, the tissue pressure was elevated. The values varied from 41 to 338 mm. of water, the lowest value being obtained in the patient with postoperative edema following the removal of a tumor of the ankle, and the highest value in the patient with scleroderma and postoperative edema.

The mean values of tissue pressure for the various groups would be misleading in that there is a great variability in the phase and extent of the edema. As shown previously, in cardiac edema[15] the tissue pressure correlated closely with the clinical state of the edema. In increasing edema, the tissue pressure increased; in subsiding edema, the tissue pressure fell. This was also found to be true in patients with other types of edema.

Discussion. The normal values for the subcutaneous tissue pressure in the volar surface of the forearm and pretibial area at heart

level were found to vary from 11 to 54 mm. of water.[15] With one exception, the values in all types of edema studied exceeded these limits. In 1 patient with postoperative edema of the foot, the value with edema was 41 mm. of water. One week later, when he was clinically edema-free, the value fell to 26 mm. of water. This illustrates the fact that patients may develop edema with a tissue pressure elevated above their original level, yet not exceeding that found in certain normal individuals. This is particularly true in receding edema.

If there is an increase in interstitial fluid, the tissue pressure must increase unless the tissues stretch equally for an equal increment in volume and still offer the same rebounding force, or unless the tissues stretch equally with each increment without a rebounding force. Since, within the limits of clinical edema, tissues do not function in this manner, the addition of interstitial fluid will elevate the tissue pressure to an extent dependent on the three following factors: 1, increase in filtration, 2, distensibility of the surrounding tissues, and 3, the rate at which interstitial fluid is removed, for example, through the lymphatics. As the fluid accumulates, tissues are displaced and the fibrous network is stretched, the tissue tension increases and this, in turn, alters the filtration and removal rates. The interplay of these three factors influences the level to which tissue pressure may rise.

The increase in filtration rate is dependent upon a disturbance in the equilibrium between the filtration, hydrostatic pressure of the small blood-vessels and the osmotic pressure of the tissue fluids, and antifiltration, osmotic pressure of the blood colloids and the tissue pressure. Changes in permeability of the capillary wall also change the filtration rate through their influence upon these factors. In cardiac edema, the essential disturbance has been ascribed to increased hydrostatic pressure; in nephrotic edema, reduction in plasma colloid osmotic pressure disturbs this equilibrium; in nephritic edema, the generally accepted explanation is an increased capillary permeability resulting in an increased osmotic pressure of the tissue fluids. As far as we know, there is no clinical state in which edema develops primarily upon the basis of reduced tissue pressure. However, in increasing edema, tissue pressure rises and becomes increasingly significant in the reëstablishment of a filtration-antifiltration equilibrium. The height to which tissue pressure may rise is dependent, as previously stated, upon the distensibility of the tissues and the rate at which interstitial fluid is removed, as well as the magnitude of pressure change disturbing the filtration-antifiltration equilibrium.

Since the tissues are imperfectly elastic, as fluid accumulates and they are stretched, they become less distensible. Tissue pressure then rises and tends to equalize the filtration pressure, acting as a limiting factor to the extent of the edema. The loss of dis-

tensibility in the skin is one of these important limiting factors. The shiny smooth stretched skin of the legs of patients with marked cardiac edema is clinical evidence of this point. With stretching and displacement of the tissues, particularly for long periods of time, these structures may lose part of their elasticity so that in receding edema abnormal amounts of interstitial fluid may be present under normal tissue pressure. This may account for our findings of normal tissue pressure in the presence of clinical edema in some of the patients in Table 1.

The third factor regulating the height to which tissue pressure may rise, the rate at which interstitial fluid is removed, as through lymphatics, has not been measured quantitatively in relationship to the other two factors. Therefore, its place and importance in influencing the tissue pressure is not established. As is well known, edema upon this basis alone does occur.

It appears that in areas with very high tissue pressures, such as in scleroderma with a tissue pressure of 338 mm. of water, or in the histamine area with a value of 246 mm. of water, with normal intravascular pressures the capillaries and veins would collapse. However, in histamine edema, the intravascular pressures are elevated locally,[2,3] and the integrity of the circulation in that area is maintained. In scleroderma, in the face of tissue pressure exceeding the normal intravascular pressure of the small vessels, the pressure in these vessels must necessarily increase to maintain the circulation. In the patient with scleroderma, before edema developed the tissue pressure determination was 280 mm. of water. One might state that the tissue pressure in this area was in the normal range but that when the fluid was introduced in the determination there was an inability of the more fibrous and less elastic structures to accommodate the increased volume, with a sudden steep rise in pressure. In such a situation, the determined pressure would not represent the actual pressure of the tissues, that is, for example, the pressure on the contained blood-vessels. Determinations of the pulse volume at heart level in the finger tip of this patient showed pulsations lower than the average normal range, both before and after sympathectomy. With development of edema and a rise of tissue pressure to 338 mm. of water, the pulsations remained essentially unchanged. Were the tissue pressure originally within normal range and elevated through introduction of edema into an unyielding tissue, the pulsations would have decreased markedly. This is evidence that the tissue pressure in this patient was actually elevated, aside from the decreased distensibility of the tissues when fluid was further introduced into them.

In tissues with very low distensibility, such as bone, calcified areas, and the epidermis, introduction of small amounts of fluid may cause the tissues rapidly to reach the state of maximum distensibility and give erroneously high results. In the tissue we have

studied, the subcutaneous area, even in scleroderma, such factors are apparently not significant with the small needle employed and negligible amounts of fluid injected.

Summary and Conclusions. In 23 patients with various types of edema, we found an elevation of the subcutaneous tissue pressure in the edematous areas. The tissue pressure was found to vary with the state of the edema.

Tissue pressure appears to be a factor in the regulation of the interchange of fluid between the blood-vessels and tissue spaces. It becomes increasingly significant with the accumulation of the interstitial fluid.

The height to which tissue pressure may rise depends upon the interplay of at least three factors: 1, increase in filtration across the capillary membrane; 2, the distensibility of the surrounding tissues; 3, the rate at which interstitial fluid is removed, for example, through the lymphatics.

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BOOK REVIEWS AND NOTICES.

THE ART OF TREATMENT. By WILLIAM R. HOUSTON, A.M., M.D., F.A.C.P. Formerly Professor of Clinical Medicine, University of Georgia; Formerly Visiting Professor of Medicine, Yale-in-China. Pp. 744. New York: The Macmillan Company, 1936. Price, $5.00.

THIS is the most interesting medical text that has come to the Reviewer's attention in several years. It is the ambition—and only too often the despair—of every teacher of medicine to impart to his students not merely knowledge, but wisdom in its application, the wisdom gained by years of experience and which is the essence of the art of medical practice. Not a few teachers are able to achieve this aim in clinical lecture or ward walk, but only rarely can this be said of the printed page. It certainly can be said of this book, and in superlative terms.

The manner of presentation is unusual, interesting and effective. The first section deals with general principles under such headings as Scope of Therapeutics, Therapeutic Thinking, Diagnosis, Honesty, Economics, The Doctor as a Therapeutic Agent; it proves the author to be not only a master clinician but also a philosopher, and a facile wielder of the pen. Then follow sections on "Patients who are to be treated chiefly by Nursing Care" (*e. g.*, typhoid fever, inoperable carcinoma); "Specifics" (animal parasite diseases, specific sera, endocrinopathies, etc.); "Conditions in which the Chief Therapeutic Method is Psychotherapy or Guidance" (the organ neuroses, hysteria, neurasthenia, etc.)—this section is superbly handled, with numerous illustrative case reports and a splendid discussion of the practicability of psychoanalysis; "Diseases which impose a Limitation upon Life as the Condition of Treatment" (obesity, heart disease, tuberculosis, old age, etc.); "Disorders in which Physiological Considerations Guide Treatment" (peptic ulcer, the diarrheas, gout, kidney diseases, etc.); and "Conditions in which Treatment is Tentative and Experimental" (the case where the diagnosis is uncertain; arthritis; allergic diseases; the neuralgias, etc.). Obviously the author "had much doubt as to classification," and his invitation that the reader challenge the classifications will call forth an abundant response [so why Hodgkin's disease and the leukemias among those for which there are specifics?], but in the main the reader will agree with the author.

There are some minor criticisms. Obviously no internist can be equally skilled in the treatment of all the diseases in this field and that is bound to produce a certain unevenness in emphasis, or at least in space allotment. So the author, a masterful practical psychiatrist, devotes 240 pages, a third of the book, to the conditions treated chiefly by psychotherapy and guidance—it is the best-done section of the book—but physiotherapy gets only half a page. The author seems unduly conservative about the serum treatment of pneumonia and too skeptical of the value of plasmochin and atabrine in malaria. There is no mention of adrenal cortical hormone on the treatment of Addison's disease, or of vaccine for the prophylaxis of whooping cough. He knows little about allergy, and much of that little "ain't so." Venoclysis certainly does not require the routine exposure of the vein by an incision. Not all would agree that diphtheria and tetanus antitoxins are the only sera of enough therapeutic value to warrant being given intravenously (what of antipneumococcic and antimeningococcic sera?). The repeated use of the word "pathology" as a synonym for "lesion" offends the purist.

The type setter has contributed an error in listing "Foot and Mouth Diseases" among the rare conditions to be treated chiefly by nursing care.

But these are trifling criticisms and should in no way detract from the value of the book as a whole. It was not written to be a mere repository of information, in which to learn at a glance "what is good for this or that," but to give a viewpoint of therapeutics, a philosophic presentation of the art of treatment, and this it does admirably. It is a masterpiece. All physicians, but especially all young physicians, and senior students should read and re-read this volume. R. K.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Vol. 4. Diarrhœa to Endoscopy of the Rectum. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc., with five assistants in a consultative capacity. Pp. 650; 129 illustrations. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, $12.00.

THE fourth volume of this noteworthy Encyclopedia embraces 42 articles, on subjects arranged alphabetically from "Diarrhœa" to "Endoscopy of the Rectum." The contributors are mostly from London and almost exclusively English. The opinions expressed in Reviews of previous volumes (*Am. J. Med. Sci.*, **193**, 711, 1937; **194**, 123, 1937) can be reiterated for the present volume. E. K.

DEXTROSE THERAPY IN EVERYDAY PRACTICE. A Survey of the Literature, 1900–1936, on the Experimental and Clinical Studies Applicable to Medicine and Surgery. By E. MARTIN, Sc.D., New York. With forewords by W. N. HAWORTH, F.R.S., Director of the Department of Chemistry, University of Birmingham (Eng.) and BERNARD FANTUS, M.D., Professor of Therapeutics, University of Illinois, College of Medicine. Pp. 451; 44 illustrations including 15 full-page plates. New York: Paul B. Hoeber, Inc., 1937. Price, $3.00.

THIS volume on a subject of interest to both practitioners and research workers forms a welcome addition to medical literature. The author has endeavored, and has succeeded exceedingly well, to correlate the more important experimental and clinical studies on the subject of dextrose therapy. There is an extensive review of the literature. The volume deals with various aspects of normal and abnormal physiology with which glucose therapy is concerned. It is often difficult to present material which is still controversial but the author has done this in an admirable manner by presenting by preference the present trend of thought rather than attempting to introduce his personal conclusions.

Besides the preface and two forewords there are fourteen chapters and an Index of Personal Names and Index of Subjects. Appended to each chapter is an excellent bibliography.

Without doubt the work will be of greater usefulness to the medical practitioner than to the research worker. There are certain aspects of the chemistry of glucose absorption which have been hastily covered and other aspects which may be proven to be incorrect, but these do not detract from the usefulness of the volume to practitioners. The chapter on "Physiological Action" on the whole forms an excellent background for those not familiar with much of the recent work which has been done. While no attempt has been made to discuss dextrose therapy in every condition where it may prove useful the many pathological conditions reviewed in the volume and the presentation of the subject matter is to be commended.

The Reviewer was especially interested in the chapter on Dextrose in Surgery which should prove very valuable. The accuracy with which the literature has been searched can be seen when he states "the value of dextrose in preventing and alleviating crises (thyroid), first realized clinically by Frazier in 1931," for a number of papers published since that time fail to mention the original paper. I. R.

FAILURE OF THE HEART AND CIRCULATION. By TERENCE EAST, M.A., D.M., F.R.C.P., Physician, King's College Hospital and Woolwich Memorial Hospital. Pp. 130. London: John Bale, Sons & Curnow, Ltd., 1937. Price, 2/6.

THIS little book contains a surprisingly comprehensive account of the various ways in which cardiovascular function may be affected by disease, together with the methods of treatment. Indeed it is almost as complete a treatise as many of the larger works on the same subject. Written from a definitely physiological point of view, the presentation is nevertheless essentially clinical and well adapted to the practical requirements of the physician in general practice. The convenience of size, however, is not an unmitigated advantage; the style is almost telegraphic which makes rather tiresome reading, while the sections on treatment are in many places so condensed that they seem unsatisfactory as a source of reliable therapeutic advice. In general, the explanations of circulatory and cardiac disorders are those currently held in this country, although recent teaching has tended to disparage the use of some of the drugs which are mentioned, particularly the proprietary extracts of digitalis. The book undoubtedly deserves recommendation to practitioners and students whose limited time precludes reference to more detailed literature.

L. L.

PATHOLOGY. (Vol. XIX of Clio Medica Series.) By E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Pp. 206; 18 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $2.00.

To survey so great a subject through all the ages in so brief a book as this must be very difficult, but the author has succeeded admirably. The slow progress through the centuries is halted, sometimes for long periods, by the positive statements of some influential figure whose certainty has blocked advance. Such was the dogmatism of Galen, which recalls the words of Goethe—"one is sure only when one knows very little about a subject." Great names stand out, sometimes of those who have made real, enduring contributions, such as Morgagni, Hunter, Cohnheim and Pasteur, sometimes of those whose engaging personalities have brought them fame and followers.

But since Pathology necessarily depends upon the advance of knowledge in all such fundamental subjects, a physics, chemistry and biology and more nearly upon anatomy and physiology, its progress must await theirs. Pathological anatomy remains necessary as the end result, but to appreciate its nature we must learn the course of events that led to its divergence from normal anatomy, and then reflect upon the disturbances that it has caused in the even trend of life. And hence it is, that while in earlier times interest was concentrated upon these distorted organs which were lightly referred to disproportions of the four humors or to dyscrasias, perhaps from the pneuma, every effort is now directed toward the discovery of the cause. More might have been said of the stirring advances of recent years, almost

always based on the etiology of disease, although the recognition of the numerous mechanisms for reaction, varying in character and intensity according to the nature of the injurious agent, and the relatively uniform mechanism of repair, has rounded out the picture.

The chronological tabulation of noteworthy contributions is of great interest, and with its aid the gradual progress may be surveyed. With this some reference to the great works on the history of medicine, such as those of Haeser, Neuburger and Pagel, etc., might have been given. But from none of these colossal volumes can one draw, as in this little book, so clear a picture of the long trail which has led us at least to the realization of an equally long road to go in the future. W. M.

Dr. Bodo Otto and the Medical Background of the American Revolution. By James E. Gibson. Pp. 345; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.00.

In 1755, Bodo Otto, then 44 years of age and a physician of repute in Germany, emigrated to America with his family. He practised medicine in and about Philadelphia until the outbreak of the Revolution when he became a military surgeon in the American Army. He served with distinction throughout the war and on its close resumed his practice in Philadelphia and Baltimore. He died in Reading in 1787. The heroic service which he rendered to his fosterland has scarcely received the recognition which it so well deserved.

The biography of Doctor Otto is the theme around which the author's narrative is expanded to include a brief but picturesque history of Hanover, pre- and post-revolutionary medicine in America, and the story of the medical department of the Continental Army with all its incredible difficulties, its bitter intrigues and its hard-won accomplishments. The reader appreciates, as perhaps never before, how large a part the ravages of epidemic diseases have played in the success and failure of the military campaigns of the past. In the light of contemporary discussion of the morality of spreading disease as a weapon of modern warfare, it is interesting to note that the British were accused of sending persons infected with smallpox into the American camp around Boston in an effort to spread infection among the troops.

This book represents an enormous amount of research into the documentary records of the period which are liberally quoted throughout. Such quotations greatly enhance its value from the academic aspect, at the same time removing it from the category of comparable works which are primarily designed to be easily read. L. L.

The Cost of Adequate Medical Care. By Samuel Bradbury, M.D. Pp. 86; 13 tables. Chicago: The University of Chicago Press, 1937. Price, $1.00.

The extensive studies conducted by the Committee on the Costs of Medical Care were concerned largely with an analysis of the expenditures for medical care in this country, with the hope of finding ways and means by which these expenditures could be reduced and better distributed. The ultimate objective of these important studies was to see what could be done to make adequate medical care available to the entire population. Calculations were made which indicated that "the cost of complete Medical Care" should be $36.00 a year per person.

Bradbury has restudied this question, and has used the study of Lee and Jones on The Fundamentals of Good Medical Care as the basis for his study, as giving the best estimate of the amount of medical care needed by the people of this country. He has translated the amount of adequate

medical service as estimated by Lee and Jones into its cost, by applying the schedule of minimum fees for medical service of the Chicago Medical Society.

The question of costs is ably analyzed from various aspects and much clear light is thrown on the annual expense of maintaining an adequate health service in this country. He comes to the conclusion that, in order to carry out a service which is thought by representative members of the medical profession to meet actually the medical needs of this country, an annual expenditure of $9,500,000 is required, instead of the $3,700,000 now expended by the American people each year for this purpose. Instead of $36.00 a year per person, which has been widely quoted as the sum needed to provide adequate medical service, actually $75.75 per person a year is required, for prevention, diagnosis and treatment of illness.

It is necessary to examine carefully Bradbury's calculations and formulations to understand this intricate problem to which he has given careful attention, and anyone interested in the economic problems of medical service must give this little volume careful reading. It is fortunate that Bradbury's study has been made before too much has been planned or erected on the insecure foundation of the previous estimates, the omissions of which are pointed out. G. R.

PHYSICAL DIAGNOSIS. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine, Chicago. Pp. 495; 298 text illustrations, and 8 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

"ANOTHER textbook of Physical Diagnosis," this one is distinguished by an excellent historical introduction by Dr. Irving S. Cutter, a profusion of well selected illustrations, and an adequate text.

In the opinion of the Reviewer, history taking cannot and should not be taught in the course in physical diagnosis as long as most medical schools teach this subject at the beginning of the second year. It is unreasonable to expect students to take anything like an adequate or even intelligent history when they have had absolutely no instruction in clinical subjects. The teaching of history taking should be part of the curriculum of the third year, marking as it does the student's first contact with the problems of clinical medicine in the Out-Patient Departments or the Wards.

It is noted with satisfaction that Dr. Sutton has successfully avoided the usual temptation to include in a textbook of physical diagnosis an abridged and almost always a useless textbook of medicine.

The ideal textbook of physical diagnosis will be written when the author confines himself strictly to the subject and when the physics of sound are adequately described and correlated with physical signs. "Norris and Landis" alone have achieved this in their physical diagnosis of the heart and lungs but they failed to realize that the human body is not bounded on the North by the pulmonary apices and on the South by the costal margins. S. L.

THE ALIMENTARY FACTOR IN DISEASE. By MAX H. KUCZYNSKI, M.D., D.Sc., Pathologist to the Ministry of Public Health of Peru; Professor of Physiopathology at the University of San Marcos, Lima, Peru, etc. Pp. 130. Second Edition of "Studies on Nutrition." The Hague: G. Naeff, 1937. Price, 3 Guilders.

IN 12 chapters the author presents his belief that alterations in nutrition are responsible for the manifestations of yellow fever, poliomyelitis, diphtheria, trypanosomiasis, baldness, gastric ulcer and appendicitis; that amyloid disease may be produced or relieved at will by alterations in the

diet and that most cellular functions "have their origin in variations of cellular nutrition." Unfortunately the specific alterations in nutrition which the author has in mind are rarely stated. Vitamin B_1 deficiency, however, is one that the author considers at some length, his contention being that, because the manifestations of this deficiency frequently resemble those of yellow fever, poliomyelitis and the other conditions mentioned above, these diseases must be due primarily to such deficiency. The author has apparently long been an observer in many fields and has exerted enthusiastic curiosity in searching for explanations of his observations. His conclusions, however, are reached through deduction rather than demonstration and therefore are not impressive; yet his monograph may be of value in stimulating careful investigation of the relationships which he suggests. Frequent typographical errors and lack of organization in presentation of the material make reading difficult. K. E.

Obstetric and Gynecologic Nursing. By Frederick H. Falls, M.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Illinois College of Medicine; Attending Gynecologist of the Illinois Research and Educational and Cook County Hospitals, etc., and Jane R. McLaughlin, B.A., R.N., Supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospitals, and Instructor in Department of Obstetrics, University of Illinois College of Medicine, etc. Pp. 492; 83 illustrations by Charlotte S. Holt. St. Louis: The C. V. Mosby Company, 1937. Price, $3.00.

The field of obstetrics and gynecology is difficult to cover in a limited space. For students this book necessarily leaves considerable material to be clarified during class instruction.

Routine abdominal palpation and resuscitation of the newborn are evidently regarded as procedures better taught by demonstration than by text book description. I believe some space could advantageously have been devoted to a discussion of present trends in obstetric analgesia.

The chapter on home delivery gives excellent directions for preparation and care during delivery. I especially enjoyed the illustrations. The well drawn sketches present important details more clearly than the usual photograph. W. E.

Gastroscopy. The Endoscopic Study of Gastric Pathology. By Dr. Rudolf Schindler, Associate Clinical Professor of Medicine, University of Chicago; Attending Gastroscopist, Michael Reese Hospital; Consulting Gastroscopist, Cook County Hospital, Chicago. With a Preface by Dr. Walter Lincoln Palmer, Associate Professor of Medicine, University of Chicago. Pp. 343; 89 text figures and 96 color reproductions of gastroscopic observations, with legends. Chicago: The University of Chicago Press, 1937. Price, $7.50.

As the first textbook in English on modern gastroscopy and as the product of one of the originators of the flexible gastroscope, who had previously had on the European continent an extensive experience with other types of gastroscopic apparatus, this work must be regarded as constituting for the English speaking profession a standard reference work. It is simply and clearly written, and includes not only what appears to be a fair statement of the history of the development of clinical gastroscopy and a detailed description of the technique for the use of the flexible instrument but also a consideration, from the endoscopist's viewpoint, of all the important

diseases of the stomach. Although further experience by the author and other gastroscopists will undoubtedly lead to many alterations of opinion as to the significance of certain observations and perhaps to a more restricted list of indications for the use of the gastroscope than Schindler in his enthusiasm now advocates, no one can question that he has developed and made available to others a method of investigation for gastric disease that rivals and at the same time supplements the Roentgen ray. The book should be read by every internist and general surgeon and it will be found indispensable to all those doing endoscopy of the stomach. T. M.

DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE. By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins University. Pp. 953, 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, $8.50.

REALIZING that neurological study of early life has not had sufficient consideration, the writer draws from his own large experience and in addition, assembles and analyzes a vast amount of relevant material. The usual anatomical classification is replaced by one primarily etiological. Appended to each chapter is a carefully selected bibliography with preference given to those references in English, and it is here, almost exclusively, that controversial subjects appear. The contents is discussed in thirteen chapters: Examination. Clinical Aspects of Anatomy and Physiology. Prenatal Diseases. Heredofamilial and Degenerative Diseases. Infections and Parasitic Invasions. Toxic and Metabolic Disorders. Vascular Lesions and Circulatory Disorders. Neoplasms. Injury by Physical Agents. Epilepsies and Paroxysmal Disorders. Diseases of the Autonomic System. Diseases of the Muscles. Syndromes and Symptom Groups. Most space is allotted to Infections and Parasitic Invasions, with the classification primarily upon etiology and secondarily upon pathological anatomy. Only those disorders are included in which it is thought the etiological agent has invaded the nervous system. Epidemic encephalitis is considered as Type A and Type B, both believed due to a filterable virus; the latter, as reported in the Japanese epidemic and that of St. Louis, 1933, clinically, appears to differ from the former. Considered in conjunction with these, is the Australian X disease, with symptoms more closely allied with Type B. However, all may be variants of the same disease. The chapter on Neoplasms and Related Conditions, is replete with case histories—thirty-one in fact. Sixty-five per cent of brain tumors, showing symptoms before fifteen years, are cerebellar in origin. During adult life, the percentage of cerebellar tumors falls, while the number of cerebral growths slowly increases. Seventy-five per cent of all intracranial tumors of childhood are gliomas; of those remaining, 13% are hypophyseal duct cysts; 5% tuberculomas; 4% pinealomas; most of those remaining are papillomas of the choroidal plexus, hemangioblastomas, meningiomas and metastatic growths. Considerable space is given to poisoning by lead, arsenic, bismuth and thallium, and rabies occupies more than four pages; but some of the functional disorders, notably hysteria—even seen in the fifth year—receive no definite consideration. Disorders of Behavior are given a heading, though discussed but little there or elsewhere. Much of the last chapter is but a repetition. However, these for the most part are minor matters. For the first time in English this excellent volume brings together the nervous disorders of infancy, childhood and adolescence, and it doubtless will become the popular book for diseases of these periods. N. Y.

NEW BOOKS.

General Hygiene and Preventive Medicine. A Text-book for College Students, Medical Students, Nurses, Public Health Workers and Social Workers. By JOHN WEINZIRL, M.S., PH.D., DR.P.H., late Professor of Bacteriology and Director of the Alice McDermott Foundation of the University of Washington; Technical Adviser on Public Health to the Washington State Planning Council, etc. Edited by ADOLPH WEINZIRL, B.S., M.D., C.P.H., Health Officer, Portland, Ore.; Clinical Professor of Public Health, University of Oregon Medical School, etc. Pp. 424. Philadelphia: Lea & Febiger, 1937. Price, $4.00.

The Therapeutic Problem in Bowel Obstructions. A Physiological and Clinical Consideration. By OWEN H. WANGENSTEEN, B.A., M.D., PH.D., Professor of Surgery of the University of Minnesota and Surgeon-in-Chief of the University of Minnesota Hospital. Pp. 360; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

Neuere Ergebnisse auf dem Gebiete der Krebskrankheiten. (Fortbildungskurs der Berliner Akademie für ärztliche Fortbildung [vom. 19 bis 26. Oktober. 1936].) Herausgegeben von PROF. DR. C. ADAM und PROF. DR. AULER. Forty-four contributors. Mit einem Vorwort von Geheimrat PROF. DR. BORST, München. Pp. 366; illustrated. Leipzig: S. Hirzel, 1937, Price, Paper, Rm. 12; Bound, Rm. 13.50.

Curieterapia in Dermatologia. By PROF. VINCENZO PALUMBO, Direttore Istituto Radioterapico Italiano. Pp. 87; 76 illustrations. Belluno: A. Salvador, 1937. Price, Paper, L. 30; Bound, L. 36.

Acta Neerlandica Morphologiæ. Normalis et Pathologicæ, Vol. 1, No. 1 (1937). Edita A H. T. DEELMAN, Prof. Anat. Pathol. Amsterdam; J. DE HAAN, Prof. Histol. Groningen; G. KREDIET, Prof. Anat. et Histol. veter. Utrecht, et M. W. WOERDEMAN, Prof. Anat. et Embryol. Amsterdam. Pp. 96; illustrated. Utrecht: N. V. A. Oosthoek's Uitgebersmaalschappij, 1937. Price: Netherl. guilders 20. per volume.

The One Hundredth Anniversary of the Army Medical Library, Washington, D. C., 1936. Pp. 130; illustrated.

A pleasant souvenir of an important occasion.

The Postmortem Examination. By SIDNEY FARBER, M.D., Associate in Pathology, Harvard Medical School; Pathologist to The Infant's Hospital and The Children's Hospital, Boston. Pp. 201; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $3.50.

Biological and Clinical Chemistry. By MATTHEW STEEL, PH.D., Professor of Biochemistry in the Long Island College of Medicine, Brooklyn, N. Y. Pp. 770; 21 illustrations and 58 tables. Price, $8.00.

The Medical Clinics of North America, Vol. 21, No. 5 (Baltimore Number, September, 1937). Pp. 318; 40 illustrations. Philadelphia, W. B. Saunders Company, 1937.

Prominent in this Baltimore number is a symposium of 10 articles on diseases of children. Hugh Young's article on the Prostate, Tillett's on the Serum Treatment of Pneumonia, Sprunt's on the Diagnosis of Liver Disease, Andrus' on Hypotension, and Wintrobe's on the Sedimentation Test will doubtless evoke especial interest.

The Roentgenologist in Court. By SAMUEL WRIGHT DONALDSON, A.B., M.D., F.A.C.R., St. Joseph's Mercy Hospital, Ann Arbor. Pp. 230. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.00.

Biological Time. By P. LECOMTE DU NOÜY, Chief of the Division of Molecular Biophysics, Pasteur Institute, Paris; formerly Associate Member of the Rockefeller Institute. With a Foreword by ALEXIS CARREL, M.D., Rockefeller Institute for Medical Research. Pp. 180; 31 illustrations. New York: The Macmillan Company, 1937. Price, $2.00.

The Olfactory Mucosa as the Arena of Combat Against Poliomyelitis. By S. Peskind, B.S., M.D., Cleveland, Ohio. Pp. 14. Cleveland: S. P. Mount Printing Company, 1937. (Price not given.)

An Outline of General Physiology. By L. V. Heilbrunn, Associate Professor of Zoölogy in the University of Pennsylvania. Pp. 603; 122 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, $5.00.

The Machinery of the Body. By Anton J. Carlson and Victor Johnson, The University of Chicago. Pp. 580; 187 illustrations. Chicago: The University of Chicago Press, 1937. Price, $4.00.

Journal of Technical Methods and Bulletin of the International Association of Medical Museums, No. XVII. Editor: Maude E. Abbott, McGill University, Montreal; Associate Editor, Robert A. Moore, Cornell University, New York. Pp. 208; illustrated. Toronto: International Association of Medical Museums, 1937. (No price given.)

This useful journal continues in this 1937 number its contributions to medical teaching, museum, photographic and histologic technique, and to pathology in general and cardiac anomalies in particular.

NEW EDITIONS.

Recent Advances in the Study of Rheumatism. By Frederic John Poynton, M.D., F.R.C.P. (Lond.), Consulting Physician, University College Hospital and the Hospital for Sick Children, Great Ormond Street, and Bernard Schlesinger, M.A., M.D. (Camb.), F.R.C.P. (Lond.), Physician to the Children's Department, Royal Northern Hospital; Physician to Out-patients, Hospital for Sick Children, Great Ormond Street. Pp. 380; 51 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Ltd., 1937. Price, $5.00.

Neurology. A Most Comprehensive and Unified View of Modern Clinical Neurology. By Roy R. Grinker, M.D., Chairman, the Department of Neuropsychiatry of the Michael Reese Hospital, Chicago; formerly Associate Professor of Neurology and Psychiatry, The University of Chicago. Pp. 999; 406 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1937. Price, $8.50.

External Diseases of the Eye. By Donald T. Atkinson, M.D., F.A.C.S., Consulting Ophthalmologist of the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas; Fellow of the American Academy of Ophthalmology and Oto-Laryngology. Pp. 718; 494 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $8.00.

The Human Mind. By Karl A. Menninger. Pp. 517; illustrated. Second edition, corrected, enlarged and rewritten. New York: Alfred A. Knopf, 1937. Price, $5.00.

Vitamins in Theory and Practice. By Leslie J. Harris, Sc.D., D.Sc., Nutrition Laboratory, University of Cambridge, and Medical Research Council. Pp. 242; 66 illustrations and 44 tables. Second edition. Cambridge: The University Press, 1937. Price, $3.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE S. JOHNSON, M.D.
PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD JUNIOR UNIVERSITY.

INSULIN SHOCK THERAPY IN SCHIZOPHRENIA.

SCHIZOPHRENIA, one of the most serious problems of mental illness confronting medicine, affects between 30,000 to 40,000 individuals annually[29] and, by virtue of its impairment of normal adaptability to ordinary everyday environments, accounts for occupancy of about one-fifth of all hospital beds in the United States.[16] Since most of these patients are supported by the State, any treatment which can increase the incidence of remissions in an ordinarily progressive habit deterioration is worthy of strongest consideration from the economic standpoint alone. From the standpoint of rendering a socially inadequate individual adequate, such a treatment should be conscientiously and critically undertaken.

Success of any therapy in schizophrenia is so often a measure of how early it is employed that early recognition of the condition is necessary. Essentially,[29] the schizophrenic reaction occurs in individuals who phylogenetically or ontogenetically are predisposed to meet poorly the various exigencies of life. Theirs is not a matter of fact acceptance or rejection of various life situations with increasing maturity and integration from successive encounters; but rather a tendency towards regressiveness and withdrawal from important concrete situations and difficulties. This is often manifest in individuals by increasing seclusiveness, excessive day dreaming and phantasy formation, abnormal interests in religion and metaphysical subjects, grimacing or silliness with odd mannerisms and incongruities of behavior. There will often be peculiar attitudes toward self and body along with various unsupported hypochondriacal complaints and delusions and hallucinations. These individuals are often overly conscientious, idealistic, with a high sense of esthetic values, rendering the every day situations of family relationships, adolescence, school, marriage, and so on, too difficult to cope with.

The result is a progressive withdrawal from these realities into an unreal world of preoccupation, projection and phantasy.

Treatment has attempted to establish rapport[8] and, through a process of reëducation and reorientation, to modify the individuals various attitudes that have been incompatible with adjustment. Assets are utilized and liabilities rationalized and the development of new and healthier habit patterns of reaction is one of the main goals. In many cases, however, loss of contact with reality is so great as to negate many of the directional efforts of psychiatrists and the establishment of any rapprochment is difficult. Various agents have been tried to produce an increasing contact and a lessened confusion and distortion of thought content. Nearly all of the employed agents have enjoyed a certain vogue and with varying success in the hands of different workers. Among these are such methods as the use of sodium amytal[3] intravenously with production of "normal lucid intervals" in catatonia varying from 4 to 14 hours, various forms of prolonged narcosis,[7] CO_2 and O_2 administration,[20,21] fever therapy with sulphur in oil[27] and convulsive therapy with metrazol.[22] All of these treatments are associated with some sort of "shock" or threat to the individual.

Among the latest and most widely publicized forms of therapy is that introduced by Sakel[25a] of Vienna. Following his successful use of insulin in combating withdrawal symptoms of morphinism[25b] and the observation that there were some beneficial personality alterations following unavoidable hypoglycemic states, intentional hypoglycemic reactions were tried in schizophrenics.

The method outlined by Glueck[11] in this country is the one generally employed and no essential modifications have been made other than those arising out of adapting the treatment to meet unpredicted peculiarities in certain individuals. Arbitrarily, four phases are delineated but essentially the treatment consists of a progressive insulinization of the patient until coma is reached, then a series of coma-producing doses of insulin are given until the patient is seen to be benefited or not improved after a reasonable length of time. This is followed by small doses of insulin in recovered or improved cases until discharged.

Normally insulin is administered at 7.00 to 7.30 A.M., the patient being under basal conditions. The initial dose is 15 to 20 units intramuscularly or subcutaneously[4], increasing 5 to 10 units daily, 6 days a week until a coma producing dose is reached which varies from 30 to 450 units.[25c] This is maintained for a general average of 30 but at times as high as 65[4] shocks. The hypoglycemic state is interrupted 4 to 5 hours after the initial injection, sufficient insulin having been given to allow for 1 to 1½ hours of coma. With remission or improvement of the psychosis, the large doses of insulin are supplanted by small (20 to 40 units) daily doses with interruption in 2 hours. This continues for about 8 days. Termination is effected by giving 150 to 200 gm. of sugar in tea, water, or milk, the patient drinking the solution in the early stages but in the coma state the solution is administered by nasal tube. Hunt and Feldman[17] find that the solution is more rapidly absorbed if well diluted and warmed. Facilities must be available for immediate treatment in cases of emergency,[4,13] and such stimulants as caffeine, coramine, adrenalin, and carbogen may be necessary, as well as solutions of glucose for intravenous use with proper apparatus for

administration. All observers stress the need of attendants who are familiar with the procedure and physicians who understand fully the principles of insulin hypoglycemia.

The symptoms of hypoglycemia in the schizophrenic are essentially similar to normal patients[19] and the descriptions of all observers correspond closely. An accurate and detailed study is that of von Angyal.[1] The usual symptoms become manifest in about one-half hour after injection by a slight drowsiness, sweating which may later become profuse, increased salivation, and acceleration of pulse rate with a rise in systolic blood pressure up to 60 mm. and a slight fall in diastolic. The ordinary shock is "wet" in type. Dry shocks in which there is no increased perspiration are regarded as ominous. As the hypoglycemia progresses, various manifestations of disturbances of the nervous system are seen. Muscular twitchings, clonic in nature appear about the face and neck, usually just before passing into coma. At times, athetoid movements and attitudes of decerebrate rigidity appear. In the coma stage normal reflexes are diminished or abolished with pathologic reflexes present such as the Babinski, Oppenheim, Rossalimo, Gordon, and others. At times, transient hemiplegias or monoplegias are seen. In deepest coma all reflex activity is abolished.

More marked and serious manifestations demanding intervention are pulse rates above 150 or below 40, vasomotor collapse, epileptiform convulsions, extreme excitement, at times accompanied by terrific hunger, severe spasm of the larynx, Cheyne-Stokes respiration and abnormally low temperatures. These latter severe manifestations are not common.

Various interesting physiologic and biochemical observations have been made. Usually the temperature drops during the shock period. Bychowski, *et al.*[4] report one of 32.2° C. In the afternoon there is at times a slight elevation. All observers note no relationship between blood sugar level and onset of coma. Kepler and Moersch[19] state that the symptoms of hypoglycemia are dependent more on the rapidity of change in the concentration of the blood sugar than on the actual amount of sugar in the blood. The blood sugar at times drops to levels below the point of accurate estimation. Electrocardiograms show slight and apparently reversible alterations, chiefly depressions of the *T* waves.[6] Hadorn[14] studied electrocardiograms on 100 patients and found changes in two-thirds similar to those found in myocardial infarction and coronary sclerosis; lowering of the *S-T* interval and lowering and negative values of the *T* wave. The changes are usually reversible and he feels they are due to an altered biochemical state, from hypoglycemia and hyperadrenalism, rather than to actual lesions. He states that the question of late effects is yet to be answered. Significant electroencephalographic changes have been noted by Hoagland, Cameron, and Rubin.[15] The pathologic picture is not clear as yet. Schmid[26] produced repeated hypoglycemic shocks in rabbits, attempting to simulate Sakel's treatment of humans. He found only minimal changes and thought these due to excess adrenalin which is increased in the blood by insulin injection. He states that he could not confirm the results of Stief and Tokay[28] who found definite cellular lesions in the brain following severe hypoglycemic shock. Grayzell[12] also produced hypoglycemic shocks in rabbits and concluded that convulsions were neces-

sary to produce cerebral lesions and the greater the number and severity the more marked the changes, consisting of shrunken cells, hyperchromasia, and corkscrewing of processes and zones of necrobiosis. Baker and Lufkin[2] in 3 patients who died of hypoglycemia found new and old hemorrhages in the brain. On 6 rabbits subjected to repeated convulsions no significant alterations were found. More work is needed. Forstmeyer[10] found no significant alterations in the hematoencephalic barrier to bromide. There is a large amount of additional work being undertaken at present which may throw light on the problem of hypoglycemia. All investigators have noticed individual differences in susceptibility to insulin and some individuals are extremely resistant to usual coma producing doses. In others, there may be a hypoglycemic reaction as long as 7 hours after termination,[5] particularly if some of the administered sugar is lost through vomiting.

Psychiatrically, the patient may manifest a variety of behavior from a drowsiness that gradually merges into coma to periods of acute and violent excitement. Often during shock there is an exaggeration of the psychosis with an increased manifestation and intensity of content. Delusions or hallucinations may become more manifest or the patient may whistle, sing, yell, moan and grimace, often making sucking movements of the lips. There is an amnesia for most of the events of the morning. At times, there may be short periods of comparative lucidity before the patient becomes comatose. Most observers in addition have noted that following termination of the shock, the patient is often in a peculiar state of suggestibility and communicability. However, attempts at any searching psychotherapy are discouraged, and, in general, the environment is made as neutral and tranquil as possible. Behavior following termination of treatment tends to correspond to that manifested at the time of interruption and this is utilized therapeutically. Cameron and Hoskins[5] have found that in paranoid patients best results are obtained when deep coma has been allowed to develop. In excited cases, termination after a few minutes of light coma, and in stuporous cases, termination during the precoma stage, so as to effect an activation of the individual. This view is in general accord with others.

Favorable cases gradually improve, their behavior becoming less bizarre, their preoccupation less and interest more. Delusions and hallucinations lose their intensity and finally disappear and insight may develop. Sakel[25d] states "the hypoglycemic state weakens, inhibits and finally represses that portion of the mind which happens to be most active at the time, so that the hitherto latent subdued and repressed elements are again brought to the surface so that they can again prevail over those which are repressed. . . . In cases which run a favorable course, the repeated hypoglycemic states finally eliminate the psychosis so that the normal personality can again achieve complete dominance."

Various theoretical formulations have been advanced, all tentatively. Sakel[25e] feels that the effectiveness of the hypoglycemic insulin treatment is due to the action of the insulin directly on the nerve itself. He feels that in schizophrenia products of the adrenal system excessively sensitize the cells of the nervous system so that normal adequate stimuli produce pathologic effects. In addition, phylogenetically ancient and

infantile nerve pathway patterns are revived, interfering with each other and producing an "intrapsychic ataxia." Insulin opposes the action of the "circulating hormone" so that excessive stimuli are muffled and the cells kept quiescent to the benefit of the individual, while the shock shatters the abnormal nerve pathways and allows the normal to again take precedence.

Glueck[11] feels that while the approach is biochemical, it is in no sense a strictly causal therapy. He is impressed with the radical generalized disturbance of vegetative, neurologic and psychic integration and a certain orderliness of manifestations in emergence from the hypoglycemic state that is meaningful and from the psychic standpoint suggest an increasing settlement of organismal and personality problems with a more specific reorientation to reality. Jelliffe[18] offers an interesting psychoanalytic interpretation. Guirard and Nodet,[13] after mentioning other shock therapies, feel that the insulin method is essentially one of shock calling forth a vital defense of the organism which effects improvement. Many observers feel that the insulin therapy of the psychoses is simply another form of shock therapy *per se* but one par excellence.

The results of treatment are very interesting. Most of the larger series are from the European investigators who report full remission rates up to 70.7% in early cases and up to 88% when the percentages of good remissions are added.[9,23,25d] In older cases the percentage of remission or improvement is lower but considerably above the expected remission rate of 20 to 30% in all cases, up to 50% in acute cases and 10% in old.[31] In the United States the percentages are lower but no large series of cases have been reported and it is too early to draw conclusions from comparative statistics.

The evaluation of results presents a problem. Rymer, Benjamin and Ebaugh[24] emphasize the need for a satisfactory method of qualitatively estimating results, feeling that more precise methods are needed. Thomas[30] asks for a settlement of the preliminary question of what one includes under the diagnosis of schizophrenia before attempting to evaluate results. Sakel[25d] defines a full remission as present when "the patient is not only symptom free . . . but has full insight into his illness . . . normal emotional reactions and that he can return to his former work." "Good" remissions represent a condition in which the patient is free of schizophrenic symptoms, but has a slight degree of defect. And finally, he speaks of social remissions in which there is improvement but symptoms persist in part. In general, these are the criteria which have been used. As any change of behavior in patients will be interpreted in the light of the observer's concepts of the disease, and as there are admitted differences in various schools of psychiatry, this aspect of the problem needs further elucidation.

GEORGE S. JOHNSON, M.D.
JOHN F. CARD, M.D.

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OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

JOSEPH C. BECK, M.D.

ASSOCIATE PROFESSOR EMERITUS, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL,

AND

M. REESE GUTTMAN, M.D.

ASSISTANT CLINICAL PROFESSOR OF OTO-LARYNGOLOGY, LOYOLA UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

RECENT ADVANCES IN PARANASAL SINUS DISEASE.

THERE is a continuously increasing interest in paranasal sinus disease if one is to judge by the large number of contributions that persist in appearing in the literature. The general tone indicates that the pendulum is swinging away from the pessimistic point of view and that a better appreciation of the functional activity of the ciliary mechanism of the mucous membranes offers a more hopeful outlook in its response to therapy. The skepticism on the part of the profession in regard to the curability is also shared by the laity and as both Black[8] and Zwerling[106] state, the patient as a rule is convinced that sinus conditions are attended by prolonged treatment, repeated operations with tedious after care and but little hope for cure. This attitude on the part of the public has not been an unmitigated evil, for it has had its rôle in guiding our attempts at therapy, both medical and surgical, in more conservative paths.

Etiology. There is an increasing appreciation of the basic rôle played by allergy in the production and maintenance of chronic sinus disease. This has been covered in detail by us in a recent review. In a review of 13 cases of asthma in which the maxillary sinuses were operated upon, De Stio[24] came to the conclusion that the poor results encountered were due to the fact that the asthma and the sinus condition were both the results of the allergic state of the patient and that the surgery would have but little influence upon the underlying allergic factor. Kelley[51] found Roentgen ray evidence of sinus disease in 89 of 100 cases of asthma that he studied. Irrigations of the sinuses rarely revealed true pus but most frequently globular masses of mucoid material. Puff[81] describes the presence of eosinophils in the nasal secretions as an indication of an allergic status. McCready[67] could also demonstrate sinus disease in 85% of several hundred asthmatic patients. Podesta,[78] in a review of the subject, also stresses the allergic nature of many cases of sinusitis. The rôle of heredity in the incidence of sinus disease is stressed by Ridpath[86] who has found sinus disease in every member and in two generations of certain families. Wood[103] feels that our method of blowing our noses might be responsible for most sinus infections. He states that tissue resistance in the nose proper is high and that in forcibly blowing our noses we tend to project the infectious secretions into the sinuses where the defensive mechanism is relatively low. He advises sniffing the secretions back into the throat along the same path the ciliary mechanism would sweep it physiologically. That blowing the nose in acute rhinitic states has frequently resulted in the production of an acute otitis media by insufflation *via* the Eustachian tube into the middle ear is an accepted fact, so Wood's assumption is not illogical. Dust-laden air as a factor in the production of sinus disease is described by Rhodes[82] who found an increased incidence in sinus disease resulting from severe dust storms in the dust bowl areas of several western states. In a review of 172 cases of antral disease Jankowski[48] was able to attribute 69% to influenza and Iwata[46] reported 2 cases of scarlet fever complicated by sinus disease. Cullom[19] believes that sinuses infected in the course of a contagious disease retain a chronic and frequently latent infection. He observed sinusitis present in 91% of cases of scarlet fever in which otitis media had developed. The sinus infection as a rule was on the same side as the involved ear. In a study of the bacteriologic findings in chronic maxillary sinusitis Enlows and Alexander[29] found the streptococcus pyogenes in 9%. The staphylococcus, both hemolytic and non-hemolytic, was found in over 70% of 64 cases by Woodward.[104]

Relation to Pulmonary Disease. The route of infection from the paranasal sinuses to the pulmonary tissues was studied by Larsell and Fenton[57] by injecting dyes into the mucosa of the frontal sinus and pharynx and following the path of the material into the lung. They found the dye to be carried into the sinus lymph spaces and lymphatics, the retropharyngeal and deep cervical lymph nodes, cervical lymphatics, subclavian vein, superior vena cava, the right side of the heart and the pulmonary capillaries.

Bronchiectasis is well known to be associated with chronic sinus disease. Watkins[102] finds that it is quite the exception to find bronchiectasis without sinusitis and claims that early diagnosis and treatment of

the sinus condition in the presence of a chronic cough will prevent its occurrence. He found the sinuses involved in 89% of 56 cases of bronchiectasis. In a series of 70 cases of bronchiectasis Kartagener and Ulrich[50] found sinus disease to be present in 56%. Leon-Kindberg and Blinder[61] report an interesting case of tuberculosis that was activated by the development of a pulmonary abscess as a complication to an acute rhinitis and maxillary sinusitis.

Arthritis. Littell[64] found a definite relationship between sinus infection and arthritis in 20 cases that he observed. He noted that the history frequently revealed that the arthritis had its onset at the time of an acute upper respiratory infection. He was able to effect improvement in 18 of his cases.

Bacteremia. In 90 cases of complications of acute sinus disease, such as meningitis, cavernous sinus thrombosis, brain abscess, and osteomyelitis, Goldman[36] found 44% of cultures taken in 37 cases to show organisms. He advises routine blood cultures in acute sinus disease as an aid in prognosticating a complication.

Diagnosis. The importance of local findings of bogginess of the nasal mucosa, and edema and swelling in and about the middle turbinate and meatus is stressed by Harper[40] in discussing hidden infections of the sinuses. He observes that not infrequently the Roentgen ray and transillumination of the sinuses may afford little, if any, evidence of sinus involvement. The value of roentgenograms in diagnosing frontal sinus disease is expressed by Lumsden,[65] although he admits that the degree of involvement cannot always be accurately determined. The accuracy of radiologic findings in antral disease was studied by Shannon[92] who compared the Roentgen ray findings with the condition noted at operation in 296 patients. In 130 cases in which a thickened membrane was found at operation this fact was diagnosed in the pre-operative films. Polypi were diagnosed in 106 cases and were found at operation, and similar corroborative findings in 22 cases with a pre-operative diagnosis of frank pus. Such a high coefficient of accuracy undoubtedly led the author to state that iodized oils as a contrast media were but rarely necessary. Ribbing[84] also states that there need be no difficulty in determining differences in mucosal thickness and polypi in sinuses free from fluid and that contrast media are superfluous. Barmwater,[7] however, is an ardent advocate in the use of contrast media and cites a number of illustrative cases. Mittermaier[71] also advocates the use of contrast media. In a study of transillumination Richards[85] has devised a method in which the element of human fallibility in judging or interpreting the degree of impairment of transillumination may be overcome by substituting a photoelectric cell for the human eye and taking direct readings from a meter. Experimentally, it was found to be superior to the roentgenogram in differentiating between varying degrees of opacity in various mixtures of pus and serum.

Effler[27] has arrived at the conclusion that the gross appearance of the irrigated material from a sinus may give some information as to the infective organism. The appearance of solid mucoid clumps in otherwise clear solutions in acute cases presaged recovery. A cloudy yellowish discharge was found to indicate a Staphylococcus aureus infection, while a cloudy white discharge indicated a Staphylococcus albus infection. A greenish tinge to the fluid was given by the presence of Bacillus

pyocyaneus, while the Bacillus proteus was associated with foul odor. Granular scanty blood tinges irrigates indicated streptococcic involvement. In chronic antral infections he found two typical irrigates; one in which slight shreds and flakes in an otherwise clear solution, indicating a mild lesion that tends to recover with conservative measures; the other, a milky, foul-odored irrigate, indicating mucosal degeneration and polypi, requiring surgical intervention for relief.

In a study of the sedimentation rate in 30 patients with chronic sinus disease, Lintz[63] found but 2 in which the rate exceeded the normal and rightfully concluded that it was of no diagnostic or prognostic value.

Treatment. An increasing appreciation of the functional activity of the ciliated epithelium has inspired an attitude of conservatism in surgical, as well as in non-surgical measures, employed in the treatment of sinus disease. Proetz[80] advises ephedrine in saline solution in acute nasal infections and isotonic solutions in sinus irrigation as having the least objectional effect upon the ciliated epithelium. He also discourages the use of oily solutions as he finds that they interfere with the normal action of the cilia and the mucous blanket. The use of mild shrinkage medicants in association with mild organic silver preparations continue to be advocated by Ashley[5] using a 0.25% neo-synephrin and a 5% neo-silvol solution. Crebbin[18] also recommended the use of neo-synephrin but advocated the use of a tampon of a 40% solution of neo-silvol. Black,[8] in addition to using tampons of 0.25% neo-synephrin, uses neo-silvol in a concentration of but 10%, which is more common practice. Fitzhugh[31] found neo-synephrin in a concentration of 0.5 to 1% to be more effective than ephedrine, and in addition it exhibited milder constitutional effects.

The use of bacterial antigens also have their advocates. In an experience extending over a period of 3 years with the d'Herelle type of bacteriophage, Ruskin[87] found it to be of value in decreasing the frequency of acute attacks. The bacteriophage was applied by tampons, nasal spray, and by instillation in the form of drops. Gundrum[37] was able to improve 32 of 36 patients with chronic sinusitis by the use of a bacterial antigen in combination with a dilute solution of neo-synephrin. He begins with the application of a 10% concentration of the antigen and gradually increases it to 100%. In a series of 62 patients treated with Krueger's bacterial antigen over a period of 3 years, Kracaw[55] observed a cure or great improvement in 52 cases. The treatment must be carried out over a period of 4 or more months. Kelly[52] also reports good results in the use of the Krueger vaccine. Fox and Harned[33] report on a novel extract of the nasal mucosa of hogs in the treatment of sinus infections. They believe that the extract gives some promise when used both orally and hypodermically.

Physical methods in the treatment of sinus disease continue to receive attention. The efficacy of various means of applying heat to the sinuses were studied by Andreen and Osborne[3] who introduced a thermocouple into the antrum and recorded the effects of the heat inducing modalities. The increase of the most efficient, showed but an unimpressive increase from an initial 98.2 and 98.5 to 99.1° F. In order of efficiency are electromagnetic field and diathermy, thermospectral lamp, Cutler water cooled lamp, compsolite, short wave diathermy and Elliott apparatus. Bryant[10] has found the Elliott apparatus of value in acute

cases but of little benefit in chronic cases. The method consists of the introduction into the nose of closed rubber tubes connected with a heating apparatus that causes the hot water to circulate through the tubes. Treatment is started with the temperature of the water at 120° F. and increased to 130° F. May[69] advises the use of the water cooled mercury lamp applied to the nose by a quartz nasal applicator, in association with infra-red therapy and short wave diathermy, in the treatment of antral infections, and Stein[96] also advocates the use of infra-red rays, diathermy and short wave as conservative measures in the treatment of acute and chronic sinus infections. Haslinger[41] also recommends light therapy in association with sweat baths. The Roentgen ray was successfully used in obtaining relief in 8 of 10 cases of acute frontal sinusitis by Lazarovits.[59] But one treatment was found necessary, applying a ½ unit skin dose.

Proetz Displacement Therapy. The use of Proetz's method of displacement therapy of the sphenoid and ethmoid sinuses continues to receive deserved attention. Laskiewicz[58] advises its routine use in the treatment of sinus disease in children and Parkinson[75] also favors its employment. The Proetz treatment given at 4- and 5-day intervals was found to be especially effective by Arslanian and Valette,[4] particularly in children. They report 15 cases with good results in all. Shambaugh[91] states that chronic ethmoiditis sometimes responds to repeated evacuation by displacement technique and Ridpath[86] found the method adequate in a case of frontal sinusitis. Shuster and Schuster[93] point out that displacement should only be used in receding stages of an acute infection. In a discussion of the value of the method Davis[22] finds that it must be used several times a week over a period of time to be effective. Nasal larvæ have been evacuated from the sinuses by Proetz displacement. Caldas[13] reports 3 cases in which he uses iodoformed paraffin oil in a concentration of 5% and Liggett[62] employed it in a similar manner for nasal larvæ. Kracaw[55] has utilized the Krueger vaccine by this method with success. Laskiewicz[58] used the antivirus by this means in treating ethmoiditis and found the infection to clear in from 3 to 5 days. Gundrum and Seminov[38] describe the results in 150 cases with definite improvement in 52%. In 16 refactory cases some improvement was noted in 11 by the addition of a stock bacterial antigen filtrate. In an additional 135 cases treated with the stock antigen in addition to ephedrine from the very onset of the treatment, improvement was noted in 64%.

Sinus Irrigation. Sinus irrigation or lavage is one of the simpler methods of treating suppuration in the antra, sphenoid or to a lesser extent the frontal sinuses. The sinuses mentioned may be entered through their natural ostia or, in the case of the antrum or sphenoid, may be perforated by a suitable trocar. In a study of the maxillary ostium in 163 adult skulls, Van Alyea[100] found that the natural orifice was easily cannulated in some 55% so that antral puncture is only necessary in about one-half of all patients seen. Sinus irrigation was able to effect a cure in 66% of 178 patients of antral disease treated by Miller.[70] Moore[72] also describes several cases relieved by irrigation. In a review of 10 years' experience at the University Clinic at Budapest, Ipolyi[45] reports that 65% of 1413 cases of antrum disease was cured by irrigation alone. Muller dos Reis[74] once more calls attention to the

accidents that may attend an antral puncture. Complications such as paralysis, amaurosis, convulsions and syncope may follow air embolism caused by the pernicious practice of expelling the irrigating fluid from the antrum by a blast of air. It is far safer to permit the ciliary mechanism and the absorptive powers of the mucosa to care for the remaining fluid than chance such a grave complication.

Surgery. By far the largest number of contributions deal with the surgical treatment of sinusitis, and mainly in the technical aspects of most interest to the operating rhinologist. For that reason many papers dealing with technical aspects of surgery will receive little or no mention in this review.

In a discussion of the indications for surgery of the antrum, Ipolyi[45] advised conservative irrigation for a period of some 6 weeks, unless the suppuration was secondary to dental sepsis, osteomyelitis of the maxilla, new growth or foreign body. By this means 65% of 1413 cases observed over a period of 10 years could be cured. This agrees well with the common experience of most rhinologists who, as a rule, consider failure of irrigation to effect a cure over a period of time as a necessary preliminary before employing more radical surgery. If irrigation fails, then an intranasal antrostomy, or window placed in the inferior meatus for better ventilation and drainage must be considered. Ipolyi found this to be necessary in 23% of the cases which were cured. Miller[70] states that in chronic infections of the antrum, ventilation and drainage are impaired due to closure of the natural ostia. He feels that the drainage of the purulent sinus secretions by gravity through the dependently placed window and reëstablishment of ventilation will permit most antral linings to recover unless grossly polypoid and diseased. Alteri[2] also feels that in many cases of chronic antrum infection the mucosa and ciliary function may return to normal if adequate drainage is provided by a large window placed in the inferior meatus. Hoover[43] advises an opening in the inferior meatus for better drainage and ventilation if the progress is unsatisfactory. He advises radical operation if the mucosa is polypoid or cystic. That the presence of marked polypoid, cystic and degenerated mucosa or that affected with other irreversible change in all probability would be but little influenced by an intranasal antrostomy, is born out by King[53] who checked the end results of 14 cases of antrum disease treated by that method. In the 5 cases in which no clinical improvement was noted postoperative examination with the Roentgen ray, utilizing contrast media, disclosed pathologic tissue. He concludes that the failure of the operation was due to the irreversible pathologic tissue.

Sinus infections with tissue changes such as these require the removal of the pathologic tissue from within the sinus before a cure may be expected. This is accomplished by a sublabial antrum operation of the Caldwell-Luc type or some modification. After removal there is a complete regeneration of the mucosa. Brownell[9] reviewed the clinical and experimental work on the regeneration of the mucosa and concludes that a complete regeneration may be expected after a period of 3 to 5 months has elapsed. The new mucosal lining is complete including ciliated epithelium. Good results may, therefore, be reasonably expected from the Caldwell-Luc procedure and Syme[97] accordingly reports that 65 of 77 patients who underwent this procedure reported

excellent results. Ipolyi[45] reports good results in all cases operated upon by the radical method. Sewall,[90] however, reports a number of recurrences with the radical operation and finds the recurrence to be due to cyst formation, partial obliteration and walled off abscesses in the sinus. He advocates keeping the opening patent so that the cavity may be observed and cleansed until complete epithelialization has occurred.

During the performance of the radical operation some of the nerves comprising the dental loops distributed to the teeth may be traumatized and there have been many reports of dental difficulty as a result of the operation. Schmidt,[89] however, in an examination of the teeth of 45 patients who had undergone 63 operations, was unable to determine any increase in sensory disturbances or in the incidence of caries. In a total of 425 teeth examined by electrical tests, but 10.8% showed prolonged anesthesia and only 2 necrosis of the root. In a similar study of the teeth with electric currents, Dahm[20] found complete anesthesia up to 6 months and hyposthesia up to 9 months. Both Dahm and Schmidt note that the state of anesthesia is in no way related to the vitality of the tooth, which is dependent on its blood supply. While damage to the dental nerves may not be entirely avoided, they may be reduced to a minimum by following the suggestion of Ehrhardt[28] who advises a high incision and removal of as little bone as possible when approaching the floor of the antrum along the facial wall.

The External Fronto-ethmo Sphenoid Operation. The conceded poor results following intranasal surgery of chronic polypoid and suppurative disease of the ethmoid, sphenoid, and frontal sinus has caused renewed interest in various types of radical operations from an external approach upon these sinuses. There continue to appear a large number of papers bearing mainly on the technical aspects of the Lynch, Ferris Smith, or Sewall types of the external ethmo-spheno-frontal operation. The whole consensus of opinion is in agreement with Futch[34] who advises a thorough trial of all less radical measures before resorting to this rather formidable procedure. He found that 4 of 6 patients with asthma evidenced improvement and 4 allergic patients were also definitely benefited. Bryant[10] reports good results in 28 cases. He performed these upon patients with extensive involvement in which there was a failure after intranasal surgery. He noted the occurrence of 3 cases of diplopia, lasting from 1 to 3 months. Wagner[101] and Daito[21] also favor the procedure and McNaught[68] admits that the radical operation may fail through the constriction of the naso-frontal opening and through the presence of pathologically involved peri-orbital ethmoid cells. Finally, Proetz[80] cautions against operations of this type that throw the sinuses into the general nasal cavity as the effect of too much air in desiccating the delicate ciliated epithelial lining. Luongo,[66] Howarth,[44] and McNaught[68] give excellent presentations of the technical execution of the operation and Yates[105] describes a skin incision that minimizes the resultant scar.

Intracranial Complications. Meningitis. In an extensive and thorough presentation of the subject of the pathways of infection in rhinogenic meningitis, Jacobsgaard[47] reports on the histologic examination of tissues of patients dying of a rhinogenic meningitis in whom no nasal operation was performed, thus leaving tissue for study intact. He found that the perineural lymphatics of the olfactory nerves and

localized osteomyelitis of the sinus structures contiguous with dura were the two important means of transmission. More light as to the possible rôle of the lymphatics of the frontal sinus in the extension of infection into the cranial cavity has been thrown by the work of Chiara and his associates[15] who were able to demonstrate the diffusion of colloidal thorium from the frontal sinuses to the meninges, the sulci, and the convolutions of the brain by both histologic and radiologic studies. Kramer and Som[56] report 10 cases of meningitis secondary to sphenoid infection. Pain in the occiput radiating to the temples and down the spine and the positive result of a sphenoid sinus irrigation aid in establishing the etiologic diagnosis of the meningitis. The authors advise intranasal exenteration of the affected sinus. Four cases recovered, 3 spontaneously and 1 after surgery. As the spinal fluid count in the recovered cases was never high, and no bacteria could be demonstrated a true diagnosis of suppurative meningitis in these cases could not be maintained. In the other cases reported bacteria were found in the spinal fluid and were associated with the fatal outcome. Field and Rogers[30] report a child dying of a meningitis which at postmortem disclosed a suppurative sphenoiditis. A new method of drainage of the basal cistern by way of the palate and sphenoid in the treatment of meningitis is advocated by Smith.[94] He utilizes a drill in perforating through the sphenoid bone and exposing the dura, which is opened to drain the basal cisterna.

Brain Abscess. Two fatal cases of subdural abscess of the frontal lobe are reported by Courville.[17] The preceding frontal sinus infection was undiagnosed in life and found at autopsy. The presence of contralateral Jacksonian attacks is a significant sign and should lead to the investigation of the sinuses as a possible source of the infection. Hoge[42] reports 2 cases of brain abscess secondary to sinus infections after swimming. One case in which signs and symptoms of cerebral involvement were slow in appearance, after a period of a month, surgical drainage was followed by a cure. In the other case a rapid course was evident, which resulted in death. The slow progress of the recovered case undoubtedly permitted encapsulation of the abscess to occur, with resultant success in drainage. Atauz and Dodds[6] report a slow developing rhinogenic frontal lobe abscess characterized by persistent headache and relative bradycardia. Surgical drainage was successful. Cavanaugh[14] reports a case of frontal lobe abscess which was operated after a period of time and successfully drained. Piquet and Delcoux[77] report a fatal case of frontal lobe abscess in which death was caused by the presence of secondary daughter abscesses in spite of adequate drainage of the primary abscess.

Osteomyelitis. In a thorough consideration of the subject, including a histologic study of 3 cases, Mosher[73] found that the marrow spaces frequently contained small abscesses and that the infection spread by the way of the diploic veins and the inner surface of the bone. He found edema of the overlying soft tissues to be the most reliable guide as to the extent of the bony involvement and that it also antedates the appearance of Roentgen findings by several days. He advocates wide excision well into the healthy bone, Jones,[49] Podesta and Carrascossa,[79] and Alonso,[1] also report several cases of osteomyelitis recovering after radical wide excision recommended by Mosher. Two fatal cases are

reported by Delcoux, Patoir and Bedrine.[23] These preceding cases were mainly complications of suppurative frontal sinus disease and many gave a history of onset after swimming. Lennon[60] reviews 91 cases of osteomyelitis of the frontal bone gleaned from the literature, and finds that the staphylococcus is the most predominating organism. He found that young adults were mainly affected. He states that the infection travels by way of the diploë and is far in advance of the Roentgen findings. Clevenger[16] reports a fatal case originating in the ethmoid sinuses and Tamura[98] reports 2 cases of osteomyelitis of the upper jaw in infants that manifested themselves clinically by swelling of the face and eyelids. Recovery followed incision with removal of the sequestrum.

Ocular Complications. Snellman,[95] in a review of sinus infections observed at the University of Helsingfors over a period of 10 years, found an incidence of orbital complications in 3%. Periostitis and subperiosteal abscess were the most frequent, and the most common offending sinus was the ethmoid. The infective organism in most cases was the streptococcus. The treatment consisted in incision and evacuation of the abscess and opening of the offending sinus. The periostitis was treated successfully by conservative measures. An extensive study of the anatomical and general findings in rhinogenic orbital disease was presented by Cordierlein, Coulouma and Van Varseveld.[12] They classify the various complications as those arising from the anterior group of sinuses producing lid inflammations, dacryocystitis, phlegmon and muscular paresis; those arising from the posterior group producing optic neuritis, ocular nerve palsies of the third, fourth and sixth nerve, and neuralgias of the sphenopalatine or trigeminal nerve. Sargnon[88] similarly describes anterior or palpebral complications of the orbit and states that they are rather benign, superficial, arising from acute fronto-ethmoid infections, yielding to a palliative management or simple external incision. The posterior or retro-orbital infections are deep seated and more serious and require surgical intervention. In a series of 38 cases of orbital infection reviewed by Burger[11] there was recovery in 35 and 3 deaths due to meningitis in 2 cases and brain abscess in the remaining one. He notes the tendency for spontaneous regression in young children. A number of authors, among them Djacos,[25] Flachs,[32] and Terrien[99] report similar cases.

There is a large number of contributions dealing with the relation of visual disturbances and retrobular neuritis as a consequence of sinus disease. As in past years many such cases have been reported in which there was recovery in vision following sinus surgery, in spite of the fact that evidence of lesions in a sinus was inconsequential or absent. In a case associated with poor vision, Halphen and Coussieu[39] were enabled to effect a return of visual function after opening the sphenoid and ethmoid sinuses in which no pathologic changes could be noted. He was unable to determine whether the restoration of vision was due to the effect of the local anesthesia, the relief of vascular stasis, by the bleeding attendant to the operation, or some other undetermined cause. Koch and McCready[54] feel that Roentgen evidence of slight haziness of the ethmo-sphenoid may indicate a hyperplasia which may be the cause of the visual disturbance. Rainey[82] reports a case of rapidly developing blindness cured by sinus exenteration during which nothing but a congested mucosa was found. Persky,[76] Genet,[35] and Durando,[26] are

but a few of the many others that report similar experiences. The most common explanation of the effects is that it is due to local depletion by bloodletting, or improvement of circulation in the optic nerve by the use of the local anesthetic or increased aëration of the sinuses. In many cases in which failure of vision to return was noted, multiple sclerosis developed at some subsequent time.

M. R. Guttman, M.D.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 25, 1937.

A Simple Synthesis of Citrulline. ALTON C. KURTZ (Laboratory of Physiological Chemistry, University of Pennsylvania). A new and superior method has been developed which permits the synthesis of citrulline in good yields directly from ornithine without the tedious intermediate preparation of ornithuric acid, α-monobenzoyl ornithine and α-monobenzoyl citrulline. The method is based upon the ability of the cupric ion to mask the α-amino groups when chelate compounds are formed with ornithine and citrulline.

Ornithine monosulphate, easily obtained by the hydrolysis of α-carbamyl arginine, is converted into its copper complex. To a concentrated aqueous solution of this chelate compound an excess of urea is added and the mixture is heated in a sealed tube at 100° C. for several hours. The insoluble citrulline copper is precipitated. This is thereafter decomposed by hydrogen sulphide in the usual manner to give 65 to 71 per cent of the theoretical amount of citrulline, calculated from the ornithine monosulphate taken. The further use of chelate formation in organic syntheses is suggested.

Relative Effectiveness of Neutron Rays and Roentgen Rays on Various Cells of the Same Organism. R. E. ZIRKLE and I. LAMPE (Johnson Foundation, University of Pennsylvania, and Department of Radiology, University of Michigan). Earlier experiments* on the comparative effectiveness of neutron rays have shown: (*a*) That for at least some cells the effectiveness of the neutrons, per unit of tissue ionization, is greater than that of Roentgen rays; (*b*) that the relative effectiveness of the two radiations is sometimes quantitatively different from organism to organism.

The present experiments extend the observations to different cells of the *same* organism. The effectiveness of the neutrons relative to Roentgen rays is greater for Drosphila eggs 3.5 hours old than for similar eggs 1 hour old. Likewise, in studies on wheat seedlings, the neutron: Roentgen ray ratio of effectiveness is greater for the root than for the shoot. Therefore it can be concluded that the relative susceptibility of different cells in the same organism is not the same for neutron rays as for Roentgen rays.

The Double Innervation of Striated Muscle. JOHN B. GAYLOR (Marine Biological Laboratory, Woods' Hole, and Johnson Foundation and Institute of Neurology, University of Pennsylvania). Opinion is divided as to the presence and nature of a double innervation to striated muscle. Physiologists generally believe that motor effects produced by the stimulation of the autonomic component are due to intramuscular vascular change. Boeke and his followers have adduced evidence pointing to an autonomic supply ending hypolemmally on the muscle fibers. Hinsey among others has failed to repeat Boeke's work and has objected to Boeke's interpretation on technical grounds. The present investigation was carried out on the striated muscle of the swim bladder of the sea robin and gives a new aspect to the problem. Sections impregnated by the Bielschowsky technique showed that the muscle had a double motor innervation: a somatic type traceable from large medullated nerves entering the muscle substance to motor terminations and an autonomic type arising from ganglia within the muscle. It is possible to see a ganglion cell with its axon giving rise to a motor ending all within the one microscopic field. Therefore the innervation of the muscle is autonomic and somatic. If, as Hinsey believes, a single muscle fiber cannot be innervated from these two different sources, two different types of muscle fiber have to be postulated according to the source of innervation. Since there is no histologic reason for such a differentiation here, since each fiber has 6 or 7 simple endings, and since the ganglionic content of the muscle is small as compared with the somatic supply, an autonomically innervated fiber is believed to receive also a somatic innervation. Although this conjecture has not yet been confirmed by the direct observation of both types of ending on the one muscle fiber, the view held by Boeke appears to fit the facts of the innervation of this particular muscle.

* Zirkle, R. E., Aebersold, P. C., and Dempster, E. R.: Am. J. Cancer, **29**, 556, 1937; Lawrence, J. H., Aebersold, P. C., and Lawrence, E. O.: Occasional Publ. Am. Assn. Advancement of Science, **4**, 215, 1937.

A Consideration of Shock in the Normal and Completely Sympathectomized Dog. N. E. Freeman, A. E. Schecter, S. A. Shaffer and H. E. Holling (Harrison Department of Surgical Research, University of Pennsylvania). A condition of shock was produced in normal dogs by means of hemorrhage. This condition was characterized by hemoconcentration, failure to respond to blood transfusion and characteristic pathologic changes in the tissues.

After total sympathectomy, even though the blood pressures were reduced to a lower level, for a longer period of time, shock was not produced. Dilution of the blood took place, there was prompt and beneficial reaction to blood transfusion and similar pathologic changes in the tissues did not occur.

The sympathectomized dogs, however, were unable to tolerate as large hemorrhages as the normal dogs. The blood pressure also fell to a lower level at an earlier period than in the normal dogs.

The difference in reaction of normal and sympathectomized dogs to hemorrhage was correlated with the peripheral blood flow. In the normal dog as the blood pressure was reduced by hemorrhage to 70 mm. of mercury the blood flow was reduced below 2 cc. per minute. In the sympathectomized dogs, at the same level of blood pressure, the blood flow was above 2 cc. per minute.

In 2 normal dogs which recovered, although the blood pressure was reduced to between 60 and 80 mm. of mercury, the blood flow continued above 2 cc. per minute. It was our impression that the absence of fear in these dogs predisposed them to recovery.

Vasoconstriction in the presence of hemorrhage, gives preferential treatment of blood supply to the vital centers, the heart and the brain. In the sympathectomized dog, such preference is lost. All the tissues of the body are accorded the same treatment. As long as the vital centers receive sufficient blood supply, all the tissues of the body probably receive an adequate amount of circulation and the condition of shock is prevented.

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VOL. 194, NO. 6 DECEMBER, 1937 NO. 789

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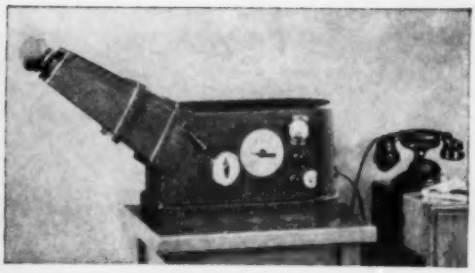

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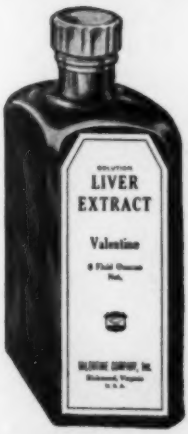

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